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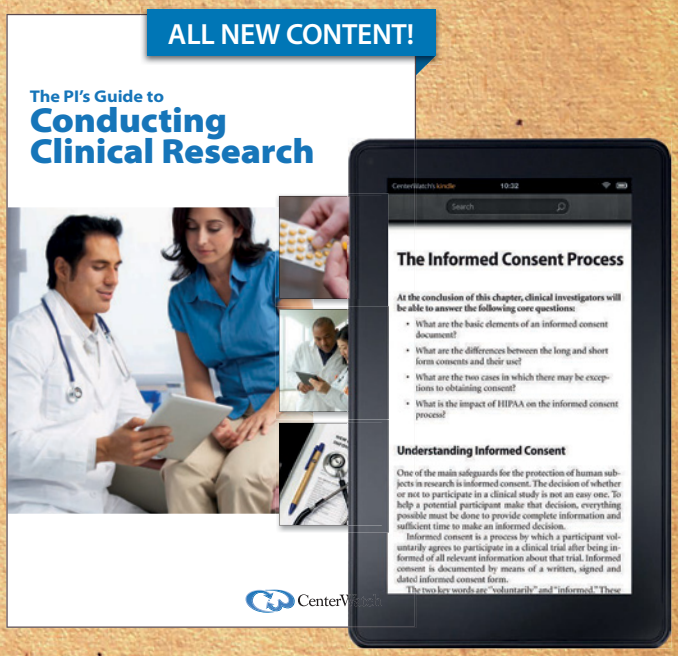

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April 2014 • Volume 28, Issue 2 • ISSN 2334-1882

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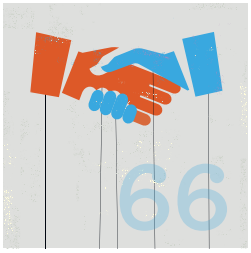

The Michael J. Fox Foundation CEO Todd B. Sherer, PhD; Co-founder and Executive Vice Chairman Deborah W. Brooks; Founder Michael J. Fox

Photo: Mark Seliger

Clinical Researcher ISSN 2334-1882 (Print) and ISSN 2334-1890 (Online) is published bimonthly. It is provided to ACRP members by the Association of Clinical Research Professionals (ACRP). The views, research methods, and conclusions expressed in material published in *Clinical Researcher* are those of the individual author(s) and not necessarily those of ACRP.

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GUEST EDITOR'S MESSAGE
Beth D. Harper, MBA

Optimizing Trial Performance

Welcome to the inaugural issue of *Clinical Researcher*. What better way to highlight the theme of "Optimizing Trial Performance" than through a newly redesigned journal? In the pages ahead, in addition to a completely new look and feel compared to our predecessor publication, *The Monitor*, including a more efficiently organized Home Study section, you will find 10 articles from a diverse collection of passionate and expert authors covering a wide range of topics related to the issue of improving trial performance. In a world of increasing protocol complexity, the need to identify smarter ways to address age-old challenges takes on even greater importance.

What's in Store

This issue will take a 360-degree view of trial optimization, first and foremost from the perspective of trial subjects and patients, as well as views from other critical stakeholders, including sites, sponsors, and contract research organizations (CROs). Although "patient-centered" has become a buzzword of late as related to trial design and execution, our lead articles by Ken Getz and Claire Meunier and colleagues remind us of the importance of taking the patient perspective into consideration when planning and executing trials.

From Ken, we gain new and interesting insights on how patients perceive clinical research. The results of a recent survey conducted by CISCRP (the Center for Information and Study on Clinical Research Participation) shed new light on opportunities to enhance subject participation by addressing their needs and concerns. Claire and her colleagues at the Michael J. Fox Foundation for Parkinson's Research (MJFF) describe how active engagement by patient advocacy associations can have a far-reaching impact on accelerating trial enrollment.

Building on the engagement theme, there is a growing recognition in the clinical research enterprise of the need for study sites to have a greater voice in the trial planning process. After all, clinical research "happens" at the site, so involving site leaders and staff in trial optimization initiatives is a critical success factor that has often been overlooked. Dr. Gustavo Kesselring and his colleagues discuss transforming one of the most flawed processes in clinical trial operations: the feasibility and site selection process. They highlight the promise of innovative technologies to streamline many study planning activities.

In my article on "Setting Studies Up for Success," I share my views and the results of extensive site needs assessment surveys to characterize what sites need and want to be successful in study execution. By asking and responding to sites' needs, we can better set research site personnel up for successful study execution.

Keeping with the theme of site-level performance optimization, Kerry Bridges and colleagues share a model and case study for validating site work effort and enjoying the benefits that come from identifying opportunities for greater efficiencies in site staff workloads.

Recognizing the importance of site engagement, two articles focus on initiatives undertaken by pharmaceutical companies to rethink their approach to site relationships to ensure more successful collaborations and outcomes. Deborah Howe and Mary Murray cover the results of an extensive site survey assessing patient recruitment support needs, and discuss how this has influenced the way that Bristol-Myers Squibb approaches the patient recruitment support process. Next, Eileen Daniel and James Denmark wrap up the discussion with the theory and practice of site engagement. They introduce new technologies for improving site interaction and provide a case study of how Endo Pharmaceuticals has applied the principles to enhance site engagement throughout the study design and execution process.

Meanwhile, trial optimization cannot occur without strong sponsor-CRO relationships, or in the absence of good performance-monitoring and measurement systems. Nikki Christison takes a fresh look at the dynamics of sponsor-CRO relationships, reminding us that sometimes innovation and optimization require going back to basics. Good clinical practices may assume an even broader definition (good *communication* practices) in an era when outsourcing the conduct of clinical trials has become the norm. Ultimately, the goal

Whether it's addressing fundamental building blocks, leveraging communications and collaborations within and amongst clinical trial stakeholders, or exploring innovative new technologies, the impact of operational improvements will always be limited if the study design is not feasible.

of all our efforts to optimize trial performance is actually to achieve a measurable improvement in the way our study results are delivered.

In his article on "Using Metrics to Measure and Monitor Performance in Clinical Trials," Randy Krauss goes back to some fundamentals of what performance metrics can and should do. He reminds us that sometimes "less is more" when it comes to monitoring and measuring trial performance, and that the most important aspect of any metrics program is not reporting them but how we respond to them.

Whether it's addressing fundamental building blocks, leveraging communications and collaborations within and amongst clinical trial stakeholders, or exploring innovative new technologies, the impact of operational improvements will always be limited if the study design is not feasible. Rounding out the discussion on trial optimization, we return to Ken Getz, whose work at the Tufts Center for the Study of Drug Development highlights the need for reexamining protocol complexity and opportunities for optimizing study designs.

Call to Action

I would personally like to thank all of our authors for their contributions—not only for the sake of our journal and its readers, but for their passionate pursuit of process improvements within their organizations and throughout the industry. A business-as-usual approach to clinical trial design and execution is simply not sustainable. We must challenge convention, take risks, try new approaches, and, most importantly, involve and engage the end-users of our studies—the patients and sites—in more meaningful ways.

Millions of patients are still waiting for promising new treatments to break through the barriers between research and development and the rest of the world. As an industry and as individuals involved in the process, we have the power to optimize the way clinical trials are performed. I hope that these informative articles inspire you to attempt similar changes within your organizations, and I encourage all of our members to share your successes in future issues of *Clinical Researcher.*

Beth D. Harper, MBA, is president of Clinical Performance Partners, Inc. and a current member of the ACRP Editorial Advisory Board. She can be reached at bharper@clinicalperformancepartners.com.

REPURPOSED FOR A NEW ERA: Why *The Monitor* is Now *Clinical Researcher*

"What happened to *The Monitor*?" you may be asking yourself as you hold this new journal with its new name in your hands. As of this premiere issue, the journal formerly known as *The Monitor* has been redesigned, rebranded, and reborn as *Clinical Researcher: The Authority in Ethical, Responsible Clinical Research.* This exciting development follows a trend that can be seen in no less a critical environment to ACRP members than the clinical research enterprise itself, where the utility of an older drug to wider audiences is frequently expanded through repurposing for a new indication.

The new era of drug and device development in which we find ourselves demands a new kind of journal. Everything that has gone into the new and already evolving *Clinical Researcher* is based on feedback from annual readership surveys, publication experts, ACRP Editorial Advisory Board members, and other stakeholders in how the very best in educational content can and should be presented to all members of the clinical research team and other key opinion leaders.

Everyone involved in bringing you the new *Clinical Researcher* is eager to hear your feedback on what has changed, what has stayed the same, and what else should or should not change in issues to come. Please send your thoughts to editor@acrpnet.org. Also, please feel free to point colleagues who are not ACRP members to http://clinicalresearcher.acrpnet.org, where they can enjoy open access to this premiere issue.

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9,500+

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8,200+

The number of clinical trials of new medicines that biopharmaceutical research companies are conducting or have conducted in collaboration with Texas clinical research centers, university medical schools, and hospitals since 1999.

2nd

National ranking of Texas in terms of the number of all clinical trials under way **(14,000+)**.

272

The number of Phase I, II, and III industry-sponsored clinical trials that were under way in late 2012 in San Antonio, Texas, home to the ACRP 2014 Global Conference & Exhibition.

Source: Research in Your Backyard: Developing Cures, Creating Jobs—Pharmaceutical Clinical Trials in Texas, a report released in March 2013 by the Pharmaceutical Research and Manufacturers of America and Texas Healthcare & Bioscience Institute.

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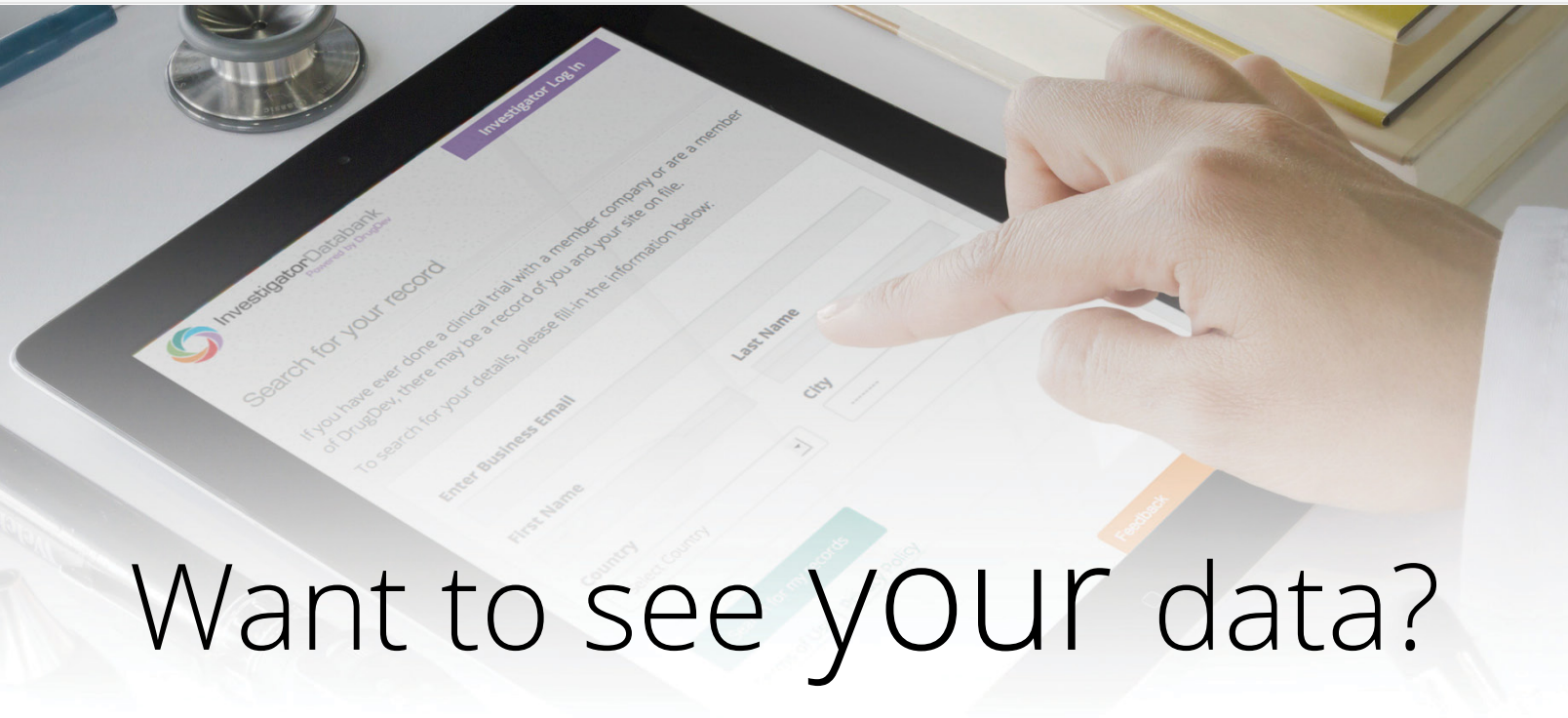

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Suzanne Heske, RPh, MS, CCRA, BCNP

An Essential Skill in Today's CRA Toolkit: Understanding CAPA Planning

There is no dispute: Over the last 15 years, the conduct of clinical trials has changed dramatically in a multitude of ways. These changes require clinical research associates (CRAs) to continually learn new skills and challenge themselves in decision making, problem solving, and flexibility.

Corrective and preventive action (CAPA) plans represent an area where the regulatory environment has changed its thinking. Documentation in the form of a note or memo to file is no longer in vogue. Regulatory agencies are clear in their expectations: Sponsors and sites must demonstrate compliance with CAPAs. Herein lies the challenge: CRAs need to acquire the knowledge and skills to understand the basic components constituting a CAPA plan and how to apply them routinely while performing day-to-day monitoring activities.

Background

CAPA plans are not a new term or concept in the Good Manufacturing Practice arena, but within the International Conference on Harmonization—Good Clinical Practice (ICH-GCP) world in the context of clinical trials, CAPAs have been increasing in popularity over the last five to eight years. CAPA requirements for clinical trials are not clearly stated in GCP guidelines, but a subsequent CAPA process is present in ICH-GCP 5.1.1 and the International Organization for Standardization (ISO) 9000.

Inadequate investigation of issues is among the top findings noted in FDA Warning Letters, and the regulatory authorities are rejecting Warning Letter responses due to inadequate CAPA plans.

In addition, the U.S. Food and Drug Administration (FDA) has incorporated language into regulations inferring the need for CAPA procedures in clinical trials (e.g., 21 CFR 312.56 and 21 CFR 812.46 in the *Code of Federal Regulations*).

More information about CAPAs makes it apparent that sponsors and contract research organizations are vigorously ramping up quality management system programs, with CAPA essentials as a core component. Why is this? Because inadequate investigation of issues is among the top findings noted in FDA Warning Letters, and the regulatory authorities are rejecting Warning Letter responses due to inadequate CAPA plans.

One of the key challenges, as evidenced by discussions at recent industry conferences, is how best to define a clinical CAPA with regard to issues that are experienced by sponsors, CRAs, and investigators during the conduct of a clinical trial. Clinical CAPAs should address issues that affect patient safety, data quality, and data integrity.[1] Les Schnoll stated that "regardless of the industry or quality system being followed, when things go wrong, an investigation is necessary."[2]

Two Sides of the CAPA Coin

Before an investigation can begin, two components of a CAPA need to be discussed: corrective action and preventive action. There can be confusion in the use of and differences between the two.

Corrective action refers to actions taken when an issue has already occurred. The intent of the corrective action is to eliminate the cause and prevent the issue from immediately recurring. Corrective action is implemented to address nonsystemic or sporadic events.

Preventive action, on the other hand, is action taken to prevent an issue or systemic problem from occurring altogether when there is perceived risk. Systemic situations are generally longstanding situations, and the remedies require changing the standard, whereas nonsystemic situations involve sudden changes to the standard, thereby restoring the situation to normal.[1,2]

Schnoll emphasizes that an effective CAPA system requires a systematic approach, consistent structure, organized procedures, and common sense. Therefore sponsors, CRAs, and investigators

Implementing a proactive approach for preventing the kinds of events that pose risks to subject safety, data quality, and integrity starts by gaining the skills and knowledge to conduct an appropriate investigation to identify root cause(s).

should avoid jumping to conclusions and remember to use their skills and experience to solve problems by asking the following questions:[2]

- What is the problem?
- Who owns the problem?
- How bad is the problem?
- What is causing the problem?
- How can the problem be fixed?
- Did the fix work (long-term sustainability)?

These questions set the framework when establishing and applying a systematic CAPA approach for addressing quality, audit, or inspection issues that arise during the conduct of a clinical trial.

Putting CAPAs into Practice

The FDA focuses on CAPA-type responses, meaning sponsors, CRAs, and investigators are actively identifying the problem, performing a root cause analysis (RCA), and then fixing the specific situation.

Laying a foundation begins with issue identification (routine noncompliance vs. serious noncompliance) in order to move the investigation process through issue causality, development of an action plan based on RCA, action plan verification, validation, implementation, and finally CAPA effectiveness checks and closure.[3]

An investigation is essential when addressing a potential issue. Implementing a proactive approach for preventing the kinds of events that pose risks to subject safety, data quality, and integrity starts by gaining the skills and knowledge to conduct an appropriate investigation to identify root cause(s). However, many organizations fall short in identifying the root cause, which may be due to insufficient training or knowledge of the processes.[3]

Determining the root cause can be achieved by instituting suitable tools, which may include a variety of methodologies: the five whys, statistical analyses, brainstorming, fishbone (Ishikawa) diagrams, and the is/is not matrix.

The is/is not matrix identifies the facts of the problem, provides a summary of the facts to test possible causes, identifies missing information, and establishes a clear borderline around the problem. This process requires input in the form of answers to questions based within the basic categories of what, where, when, how (to what extent), and trends.[2] Once this information is identified, individuals will have a good understanding of where to focus when determining if the root cause is the actual perpetrator to continuing in the CAPA process.

After actions are implemented, the next step is to allow for a period of evaluation, including continual review. The evaluation may focus on ensuring appropriate CAPA implementation and on measuring the effectiveness and long-term sustainability of the actions. A follow-up audit or assessment is a good means for determining whether the CAPA ultimately produced the desired outcome.

Conclusion

As practices within the industry evolve, the expectations of regulatory agencies will become more apparent with regard to clinical CAPAs. "The FDA wants clinical trial sites to prove their compliance with regulations through better documentation of corrective actions," one expert says.[4] With this in mind, CRAs need to prepare themselves as well as guide their sites on how to implement and carry out effective CAPA plans.

CRAs can build upon their skillset by finding resources (online or in institutional libraries) on any of the key subjects noted throughout the content of this column. Understanding the elements of a robust CAPA plan (including identifying the actual root cause of the issue and developing/implementing effective actions) has become an essential skill in the toolkit of today's CRA.

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In this issue of *Clinical Researcher*, three articles have been selected as the basis for a Home Study test that contains 30 questions.

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ARTICLES FOR THE TEST

The April 2014 *Clinical Researcher* Home Study is based on the following three articles in this issue:

1. **New Insights into Study Volunteer Perceptions and Experiences to Inform Patient-Centric Clinical Trials**

   Kenneth A. Getz, MBA, Chairman and Director of Sponsored Research, Center for Information & Study on Clinical Research Participation, and Associate Professor, Tufts Center for the Study of Drug Development, Tufts University School of Medicine, and CenterWatch founder and owner, and Metrics Champion Consortium co-owner

2. **Accelerating Drug Development for the Field: Building Clinical Trial Recruitment Infrastructure in Parkinson's**

   Claire C. Meunier, MBA, Director, Research Partnerships; **Sohini Chowdhury, MA,** Senior Vice President, Research Partnerships; **Lily W. Cappelletti, MPA,** Associate Director, Research Partnerships; and **Todd B. Sherer, PhD,** Chief Executive Officer; all at The Michael J. Fox Foundation for Parkinson's Research

3. **Opportunities to Optimize Study Design to Drive Development Performance and Efficiency**

   Kenneth A. Getz, MBA, Chairman and Director of Sponsored Research, Center for Information & Study on Clinical Research Participation, and Associate Professor, Tufts Center for the Study of Drug Development, Tufts University School of Medicine, and CenterWatch founder and owner, and Metrics Champion Consortium co-owner

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Optimizing Trial Performance

OPEN BOOK TEST

This Test Expires on April 30, 2015

Original Release Date April 28, 2014

LEARNING OBJECTIVES

After reading these articles, participants should be able to:

1. describe public and patient attitudes and perceptions about clinical research and how they have changed over time.
2. discuss the critical role diverse stakeholders play in the process of clinical trial recruitment and describe select innovations in the clinical trial recruitment process.
3. characterize protocol design practices, the ways that complexity has increased over time, and new approaches to improve study design.

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New Insights into Study Volunteer Perceptions and Experiences to Inform Patient-Centric Clinical Trials

PEER REVIEWED | Kenneth A. Getz, MBA

[DOI: 10.14524/CR-13-00061R1.1]

Stakeholders in the clinical research enterprise have stepped up their efforts to place patients at the center of clinical research planning and execution. Among the many ways that patient-centric clinical research is progressing, clinical research professionals are partnering with patients to play a more active role in informing and shaping protocol design feasibility, and site staff are engaging with their local stakeholders to encourage community support for clinical trials and to attract more local volunteers into studies.

Despite this growing emphasis on patient-centered and -directed clinical research, it has been more than five years since an assessment of public trust in regulatory agencies and pharmaceutical companies has been conducted,[1] and more than eight years since a comprehensive global assessment of changing public and patient perceptions about clinical research has been performed.[2]

Framing the Study

In response, between January and March 2013, the Center for Information & Study on Clinical Research Participation (CISCRP), an independent nonprofit organization, developed and conducted the "2013 Perceptions and Insights Study" to reestablish routine global assessment of public and patient perceptions, motivations, and experiences with clinical research participation. In doing so, CISCRP hopes to assist the clinical research enterprise in monitoring trends and identifying opportunities to better educate and engage the public and patients as stakeholders and partners.

The online study was conducted among a global community of health information seekers and research participants. Having now collected nearly 6,000 completed surveys, CISCRP's study is one of the largest international clinical research surveys ever conducted.

Overall, the study results show significant improvement in public perceptions of clinical trial safety, trust in the motives of research professionals, and appreciation for clinical trial volunteers. However, the results also reveal numerous areas where clinical research professionals are missing opportunities to better engage study volunteers and to optimize recruitment and retention. This article summarizes the key findings from this major study.

Study Methodology

CISCRP conducted the "2013 Perceptions and Insights Study" online, based on a pilot assessment of public and patient preferences with regard to questionnaire completion. The survey instrument included questions posed in past surveys conducted by Harris Interactive and CenterWatch, as well as new questions. Representatives from pharmaceutical and biotechnology companies, contract research organizations, and investigative sites provided input into the survey instrument design. The final survey instrument was reviewed by a central ethical review committee.

CISCRP collaborated with Acurian—a global provider of patient recruitment and retention services—for its help in reaching and engaging respondents around the world. Acurian maintains a proprietary database of people who have explicitly opted-in—via online and offline consumer health surveys—to receive healthcare information on specific diseases and clinical trial notifications.

A total of 5,701 international respondents completed the survey, with the highest concentration (75%) based in North America; 15% in Europe; 5% from South America; and another 5% from the Asia-Pacific region. A majority of respondents (58%) were female, and approximately four out of 10 respondents had participated in a clinical trial

LEARNING OBJECTIVE
After reading this article, participants should be able to describe public and patient attitudes and perceptions about clinical research and how they have changed over time.

DISCLOSURES
Kenneth A. Getz, MBA: Founder and owner of CenterWatch.

prior to completing the online survey. Respondents diagnosed with an illness represented a very broad mix of disease indications. Two-thirds of respondents were 45 or older, with the overall respondent age distribution as follows:

(6%) 18–24 years old;
(12%) 25–34 years old;
(17%) 35–44 years old;
(23%) 45–54 years old;
(26%) 55–64 years old;
(12%) 65–74 years old;
(4%) 75 or older.

Throughout this report, generally a three-percentage point difference between subgroup values is significant at the $p < .05$ level.

The study gathered results on far more topical areas than space allows for examination in this article. Please refer to www.ciscrp.org to receive a comprehensive series of reports on the study results.

Discussion

HOW PEOPLE PERCEIVE AND UNDERSTAND CLINICAL RESEARCH

Public perceptions of clinical research appear to be improving. This may be due to a number of factors, including outreach and educational efforts implemented by CISCRP and other organizations, as well as more widespread coverage of clinical research in social and digital media communities. The proliferation of general clinical research information and listings of active clinical trials in print and online, and recent efforts to improve the transparency and dissemination of clinical trial results, may also be contributing to this shift in public and patient perceptions.

Public trust and perceived safety

Whereas 45% of all respondents said that they did not trust research sponsors to inform the public quickly about safety concerns in 2005,[2] only 28% do so in the 2013 study.

A very high percentage of current respondents believe that clinical research studies are "Somewhat Safe" (58%) and "Very Safe" (36%). Only 2% of North Americans believe that clinical research studies are "Not Very Safe" and "Not at All Safe," compared to 17% of the European public and 12% of the Asia-Pacific public sharing this view. In South America, one in five perceives that studies are unsafe.

Perceptions of clinical research study safety are also a function of age, with a significantly higher percentage (14%) of 18- to 44-year-olds perceiving that studies are unsafe ("Not Very Safe" and "Not at All Safe").

Improvements in public sentiment were observed in several areas (see Table 1). Although nearly half of the public agreed with the statement that study volunteers are gambling with their health in 2005,[3] only 23% agreed in the 2013 study. Also, whereas 46% of the public agreed with the statement that "participants are 'experimental test subjects' and NOT people" in 2005, only 34% agreed with that statement in the most recent study.

General knowledge

Overall, individuals from a high proportion of the public (81%) consider their general knowledge about clinical research to be "Somewhat" or "Very" informed. A significantly higher proportion of the public in regions outside North America consider themselves less informed about clinical research, with 28% in Asia-Pacific, 31% in South America, and 47% in the European Union indicating that they are "Not at all informed" and "Not very informed." Further, 18- to 34-year-olds consider themselves poorly informed, and 55-year-olds and up believe that their general knowledge about clinical research is well informed (more than 85% consider themselves "Somewhat" or "Very" informed).

Recent efforts to improve the transparency and dissemination of clinical trial results may be contributing to this shift in public and patient perceptions.

TABLE 1. Tracking Improvements in Public Perceptions

Percent who indicated "Strongly or Somewhat Agree" that people who participate in clinical trials:	CISCRP 2013 (US)	Harris Interactive 2005 (US)
Get access to the best doctors	61%	46%
Get access to the best possible treatment	62%	48%
Are like experimental test subjects NOT people	34%	46%
Make a contribution to science	88%	86%
Have a chance to receive free medicines and care	76%	65%
Are gambling with their health	23%	49%
Learn more about their condition and health	84%	76%
Source: CISCRP, 2013 Perceptions & Insights Study	*N = 5,701*	*N = 2,935*

Perceived benefits and risks of participation

Altruistic reasons, including advancing science and medical treatments and helping to improve and save lives, top the list of perceived benefits of participation. One in seven perceives improvements in one's own medical condition as a top benefit. A small percentage overall (5%) perceives monetary compensation as a top benefit. A significantly higher relative percentage (10%) of the European public rates compensation as a top benefit, and a significantly higher percentage of the South American public (7%) rates free medical care and attention as top benefits.

The area of highest perceived risk of participation overall is the possibility of side effects. Some regional differences in perceived risk are evident, with the South American and Asia-Pacific public rating risks to overall health and the disclosure of private medical information higher than their counterparts in North America and, to some extent, in Europe (see Table 2).

TABLE 2. Top Perceived Benefits and Risks

BENEFITS	OVERALL	North America	South America	Europe	Asia-Pacific
Advance science and treatment	33%	35%	25%	26%	23%
Help improve or save lives	29%	30%	20%	28%	21%
Help improve my condition	15%	16%	6%	11%	13%
RISKS	**OVERALL**	**North America**	**South America**	**Europe**	**Asia-Pacific**
Possibility of side effects	57%	59%	45%	53%	42%
Possible risks to my overall health	20%	19%	24%	27%	21%
Possibility of receiving placebo	13%	14%	10%	7%	14%
Possible disclosure of my private medical information	5%	3%	13%	8%	13%

Base: N=5,701 Respondents
Source: CISCRP, 2013 Perceptions & Insights Study

Willingness to participate

With respect to general public willingness to participate in a clinical research study, overall the results of the 2013 study are consistent with those from past surveys. A very high proportion (87%) of the public says that it is "Somewhat Willing" and "Very Willing" to participate in a clinical research study. A significantly lower level of willingness to participate is evident among the public outside North America, with the corollary that a much higher percentage of the public in Asia-Pacific, South American, and European regions are "Not Very Willing" and "Not at All Willing" to participate: nearly one-fifth of the Asia-Pacific public, one-fourth of the South American public, and one-third of the European public.

Meanwhile, 18- to 34-year-olds indicate that they are the least willing of all age groups to participate in a clinical research study, with 21% saying that they are "Not Very Willing" and "Not at All Willing" to participate.

HOW PEOPLE LEARN ABOUT CLINICAL RESEARCH STUDIES

Sources of information

More than half (52%) of survey respondents prefer healthcare professionals—primary and specialty care physicians—as their source of clinical research information. Only a relatively small percentage (20%) of the public, however, actually receives information from these sources. Approximately one in four prefer receiving clinical research information from pharmacists and patient advocacy groups, but a very small percentage (8% and 11%, respectively) of the public actually does so.

The Internet and the media (e.g., newspaper, radio, television) are the top sources actually used by the public and patients to find clinical trial information. Nearly half (46%) of respondents indicated that they used the Internet; 32% indicated that they used e-mail; and 39% indicated that they used the newspaper, radio, and television.

A significantly higher percentage of the public in South America and in the Asia-Pacific region (33% and 26%, respectively) indicated that family is a top preferred and actual source for clinical research information. Among the public in the North America region, preferred and actual sources for clinical research information were higher in nearly all areas (e.g., Internet, e-mail, traditional media, advocacy groups), with few exceptions.

A significantly higher proportion (46%) of the North American public reported that "snail mail" is a top source for clinical research information, whereas only 5% of the public in Europe and 9% in Asia-Pacific reported receiving clinical research information from this channel.

Trends in the sources for clinical research information parallel broader changes associated with the growth and proliferation of digital and social media. Use of the Internet as a top source for clinical research information has increased significantly, while the use of the more costly traditional mass media has declined steadily over time.

The results of the 2013 study indicate that overall use of social media to reach prospective study volunteers remains low at this time, particularly as

Use of the Internet as a top source for clinical research information has increased significantly, while the use of the more costly traditional mass media has declined steadily over time.

targeted toward the European and North American public. Also, nearly 60% of the respondents reported that they have not used social media to learn about clinical research. Of those who have used social media, Facebook and message boards were the top sources. Wide regional differences in social media use are evident.

Not surprisingly, use of social media for clinical research information is also a function of age. A significantly higher percentage of 18- to 34-year-olds (62%) have used social media, with Facebook and YouTube topping the list of media used. The vast majority of the public older than 55 have not used social media to learn about clinical research.

HOW PEOPLE EXPERIENCE STUDY PARTICIPATION

Factors influencing enrollment

Among respondents who have participated in a clinical study, access to quality care and to medical experts top the list of important factors that influenced the decision to participate, with the highest percentages for these factors observed among women and North American study volunteers. Nearly all (90%) women who have participated rated these two factors "Somewhat" or "Very" important to their decision to enroll in a clinical study, compared to 79% of men. Whereas nearly 90% of North American clinical trial participants said that access to quality care and to medical experts was "Somewhat" or "Very" important to their decision to enroll, only 55-63% of the European, South American, and Asia-Pacific public rated these factors as important influences (see Table 3).

Learning about one's illness is also rated as a top factor influencing the decision to participate by 84% of North American study participants. A high percentage (71%) of study participants overall—73% of the North American public, 55% of the European public, 68% of the South American public, and 59% of the Asia-Pacific public—rated the prospect of receiving clinical trial results and regular updates about the research during the study as top factors influencing their decision to participate. These two factors are among the highest factors influencing South American and Asia-Pacific study volunteers to participate.

TABLE 3. Importance of Factors Influencing the Decision to Participate

		GENDER		REGION			
Percent rate "Somewhat/Very Important"	Overall	Female	Male	NA	SA	EU	Asia-Pacific
Quality medical care	85%	90%	79%	90%	55%	61%	58%
Access to medical professionals	83%	88%	78%	88%	57%	63%	57%
Learn about my disease	79%	83%	74%	84%	47%	55%	59%
Receive regular updates about the research while I'm enrolled	68%	70%	66%	71%	59%	52%	57%
Receive information about the results after the study has ended	71%	73%	69%	73%	68%	55%	59%
Feel part of a community	61%	65%	57%	62%	63%	57%	53%

Base: Have Participated (N=1,724). Source: CISCRP, 2013 Perceptions & Insights Study

Overall, the study results show significant improvement in public perceptions of clinical trial safety, trust in the motives of research professionals, and appreciation for clinical trial volunteers.

Overall expectations and experience

The majority (three out of four) of study volunteers overall reported that their study met their expectations, and the remaining quarter of them felt that their study "did not meet" or "fell short of meeting" their expectations. Differences in participant expectations varied widely by gender, age, and region. Whereas 70% of South American study volunteers reported that their clinical study exceeded their expectations, only 24% of North Americans reported sharing that view.

Factors influencing retention

Top factors most motivating study volunteers to continue to participate in their clinical trials include compensation (35% rate this a top factor) and the desire to uphold one's promise or commitment to remain in the study (34%). Positive response to the investigational treatment (26% rate this a top factor), free study procedures (26%), and information learned about one's condition (24%) are second-tier factors influencing volunteer retention.

Post participation

The overwhelming majority (95%) of study volunteers said that they would consider participating in another clinical research study in the future, an increase of 10 points since 2007.[4] A significantly higher percentage of North American (97%) and Asia-Pacific study volunteers (93%) would consider participating in a future study than in other regions. One out of four study volunteers in South America and one out of five in Europe would not consider participating in a clinical research study in the future.

A significantly lower percentage (82%) of 18- to 34-year-olds would consider participating in a future study. The unique attitudes, perceptions, and experiences of study volunteers in this age group suggest that customized education and engagement strategies are needed (see Table 4).

TABLE 4. Unique Profile of 18- to 34-Year-Old Study Volunteers

	All Respondents	18- to 34-year-olds
Agree that clinical trials are "Not Very Safe" or "Not at all Safe"	6%	14%
Who used social media to learn about clinical research	41%	62%
Who found the informed consent form "Somewhat Difficult" or "Very Difficult" to understand	19%	49%
Who felt that their site visits were "Somewhat Stressful" or "Very Stressful"	20%	51%
Who would not consider participating in another clinical trial	5%	18%
Who, after the trial ended, report speaking frequently with others about clinical research	12%	38%

Base: N= All 5,701 Respondents. Source: CISCRP, 2013 Perceptions & Insights Study

INELIGIBLE PARTICIPANTS

Respondents recalled a rich variety of reasons they did not qualify for their clinical trial. Among individuals who were not eligible to participate, however, more than a third indicated that they did not know why they failed to qualify. Modest differences by region are evident; the highest percentage (37%) of Europeans indicated that they did not know why they failed to qualify. Differences by age were also observed, with a significantly higher percentage of 18- to 34-year-old (40%) and 75-plus-year-old (43%) study participants reporting that they did not know why they were ineligible.

A shocking two-thirds of study volunteers who failed to qualify are lost to the clinical research enterprise either temporarily or permanently. Nearly one out of four volunteers (23%) who expressed interest in participating in a clinical trial but was deemed ineligible decided not to pursue another clinical trial. More than four out of 10 (42%) of such study volunteers overall reported doing "Nothing" in response (see Figure 1).

The high incidence of ineligible study volunteers who choose to discontinue searching suggests opportunities to educate study volunteers when they learn that they have not qualified for a given trial, and to provide more proactive assistance in identifying relevant trials given their initial interest.

Conclusion

The results of the "2013 Perceptions and Insights Study" build on prior public and patient polls conducted eight years ago, and set new baseline measures from which to make future comparisons. The results indicate that public trust in, and attitudes about, clinical research have improved, as have public knowledge and awareness of clinical research. The results shed light on regional public and patient differences, suggesting new ways to customize study conduct practices and recruitment and retention tactics. Study findings also reveal numerous new ways to optimize recruitment and retention performance.

CISCRP plans to conduct this international study every other year, in order to monitor changes in public opinion and patient experiences when participating in clinical research. We welcome ideas and input into ways that the survey instrument can be improved. The study is part of a broader series of research that CISCRP conducts annually on public and patient attitudes, behaviors, and experiences to derive substantive and actionable insights that clinical research professionals can leverage to more effectively engage the public and study volunteers.

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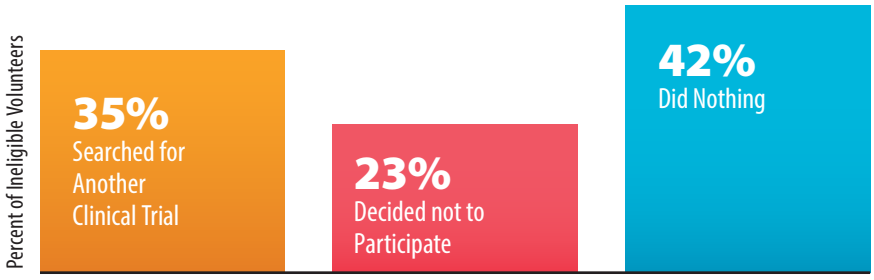
FIGURE 1. Losing Ineligible Volunteers



Base: Volunteers Who Wanted to Participate But Did Not Qualify (N=2,647). Note: One-third of all volunteers "don't know" or can't recall why they didn't qualify. Source: CISCRP, 2013 Perceptions & Insights Study

Accelerating Drug Development for the Field: Building Clinical Trial Recruitment Infrastructure in Parkinson's

PEER REVIEWED | Claire C. Meunier, MBA | Sohini Chowdhury, MA | Lily W. Cappelletti, MPA | Todd B. Sherer, PhD

[DOI: 10.14524/CR-13-00066R1.1]

LEARNING OBJECTIVE
After reading this article, participants should be able to discuss the critical role diverse stakeholders play in the process of clinical trial recruitment and describe select innovations in the clinical trial recruitment process.

DISCLOSURES
Claire C. Meunier, MBA; Sohini Chowdhury, MA; Lily W. Cappelletti, MPA; Todd B. Sherer, PhD: Nothing to disclose.

There is no "department of cures."[1] There are many diverse players involved in drug development, each of whom brings critical financial, intellectual, and human resources to the process. However, no one is in charge of the overall direction the field takes—charting the course and addressing challenges as they arise.

Recognizing this, the Michael J. Fox Foundation (MJFF) for Parkinson's Research endeavors to play this role for Parkinson's disease (PD), a progressive neurodegenerative condition characterized by slowness in movement, gait problems, rigidity, and tremors. The foundation's singular focus is to develop new therapies and, eventually, a cure for this condition.

As the world's largest nonprofit supporter of Parkinson's research, MJFF has funded more than $450 million to date to bridge the translational research gap. The foundation combines this funding with intellectual resources, person power, a venue for collaboration, and leadership of the field to objectively address key roadblocks in drug development for PD.

Although the research the foundation has funded to date is a critical contributor to its impact, the thought leadership, staff-directed activities, and collaborative discussions it facilitates are also vital in accelerating the course of drug development in PD. MJFF is constantly scanning the PD landscape to determine systemic trouble spots for the field and, where it is clear that the foundation can play a role, quickly deploying resources to address them.

Focus on Trial Recruitment

Clinical trial recruitment emerged as a priority over the last three to five years, as the understanding of the underlying biology and genetics of PD increased dramatically. These new findings have spurred more activity than ever before to develop new therapies to improve PD symptoms and to slow or stop the progression of the disease. Consequently, treatments aimed at new targets are moving swiftly through the drug development pipeline and beginning to enter clinical testing.

Seeing this unprecedented activity approaching the clinic, the foundation acknowledged an opportunity to enhance the PD risk profile to make it more attractive for industry to test promising compounds. MJFF has since prioritized opportunities to identify strategies to decrease the time and cost it takes to conduct a trial.

Like trials in most other disease states, PD trials are chronically slow to recruit. Across central nervous system (CNS) disease trials, there is an average 116% increase in the enrollment timeline to fully recruit a study—more than double the timeline set at the study start.

About 37% of sites in a CNS trial underenroll, which increases the recruitment burden of high-performing sites and often requires unplanned time and investment to activate new sites. The average enrollment rate in CNS studies averages .85 subjects per site per month.[2] Also, the costs associated with recruitment, not to mention extended recruitment timelines, are staggering. Anecdotally, sponsors budget $3,000 to $10,000 per enrolled subject for recruitment alone.

Thus, recruitment is one of the most costly and time-consuming aspects of testing compounds in humans. This, combined with the unique patient and research community constituents we work with, makes trial recruitment a prime opportunity for focus.

This article addresses the challenge of clinical trial recruitment in PD, describes patient and site/

sponsor strategies that the foundation has implemented, and shares outcomes on the progress of these efforts to date. Although the learnings, examples, and outcomes provided here are all specific to MJFF's experience, many lessons are likely applicable to other organizations and diseases.

Why is Participation in Trials So Poor?

The foundation's due diligence to date on recruitment targeted three key stakeholders in the trial enterprise—the patient community, trial sites, and study sponsors—and identified key challenges and deficiencies in each group to inform programmatic design.

PATIENT COMMUNITY

Successful clinical testing of a new therapy requires patients to play a role that no one else can play. No matter how many dollars, brilliant researchers, hours, and goodwill go into planning a trial, there comes a moment when the sites are activated, the clinic doors open, and patients are literally the only players who can move things forward.

In 2011, MJFF began due diligence with an informal survey of 832 patients to better understand their knowledge of trials and their perceptions about them. The results indicated that less than one in 10 PD patients had participated in a trial, although more than 80% of respondents were at least "somewhat likely" to be willing to participate in one.

In exploring this further, three key needs in the patient community emerged: awareness building about the need for people to participate, education about what a trial entails, and an easy action step to actually find a trial in which to participate.

The survey shed light on the need for awareness: 39% of respondents in the survey stated that "clinical trials for Parkinson's have little trouble recruiting volunteers." Patients will only know that trial participation is possible when they are aware that a trial is happening and recruiting volunteers.[3]

Clearly, knowledge is lacking within the patient community that trials struggle to recruit, and this key underlying principle must be communicated widely. Such a lack of awareness may stem from the fact that clinical trials are not part of the standard dialogue between a patient and treating physician. This is especially true if the treating physician is not also conducting research, which makes it even less likely that the physician will integrate discussion of trial participation into a patient's visit.[4]

Once patients are aware they are needed, education on what it means to participate is important. The survey findings included the following:

- 46% of respondents stated they believed it was true that patients in clinical trials are "guinea pigs"
- 32% believed that participating in a trial meant exposure to experiments to which they did not agree
- 33% stated that participation in a trial would interfere with their usual care

Such common misconceptions must be addressed and demystified to increase willingness and convert awareness into active trial participation for most people.

Once aware and "primed" through broad education about what is involved in trial participation, the final, and perhaps most important, step is providing an easy action item that people can follow to find out about specific trial opportunities that are a good fit for them on an ongoing basis.

As the world's largest nonprofit supporter of Parkinson's research, MJFF has funded more than $450 million to date to bridge the translational research gap.

The resource most often cited to find trials across all diseases is ClinicalTrials.gov. Although this is a useful tool for select purposes, and one many patients use to find trials, it has several shortcomings, making it ill equipped to serve this specific purpose: The language used on the site is very scientific; searches cannot be tailored to a patient's profile; and recurring alerts about new trials are not possible. ClinicalTrials.gov is an immense resource, but it was simply not built to serve as a recruitment portal or to be a resource for the general public.

Better solutions must be developed to better meet the patient community's need to access information about currently recruiting trials for which individuals might qualify.

TRIAL SITES AND STUDY SPONSORS

Of course, patients are just one part of the equation. They have to have somewhere to go, and they need the system and processes set up to receive and enroll them into a study. Sites and sponsors play an equally important role in addressing this challenge in the trial ecosystem.

Sites are faced with many barriers to recruitment, some involving logistical and operations hurdles, and others in the realm of strategy and core skills. At its very foundation, clinical trial recruitment is a sales and marketing activity. Often, and importantly so, site teams working on a study have science and medical training. However, at the recruitment stage of a trial, strategic marketing, planning, and sales tactic implementation are needed most.

Additionally, sites tend to have a standard approach to recruitment for all trials: Tagging charts and recruiting from an investigator's panel of patients is the classic recruitment plan for a site starting a trial. Some sites may have plans for outreach to their physician colleagues, speaking at support groups, or center newsletters as part of their standard study start plans, as well. Rarely, though, is the recruitment plan for a study tailored to the "target patient" a study plans to recruit. Even more infrequently is a plan mapped out by a site prior to study start. Such factors make it difficult for sites to budget for and justify funding for novel tailored strategies appropriately.

In this environment, study sponsors also play a critical role. On the one hand, recruitment is a prime expense and concern; on the other, sponsors leave much of this up to the sites. In the typical multisite study, a sponsor may provide recruitment materials and some funding for advertising, but otherwise does not spearhead the development of a tailored recruitment plan or work with individual sites to determine how best to implement it locally.

Volunteers and trial teams are matched to one another through the website's proprietary algorithm, which takes into account an individual's profile and the profile of the volunteer that each study is looking for.

The kind of resources and support sponsors provide plays a significant role in the trial recruitment ecosystem, often leaving sites underfunded and ill-supported to execute on strategies that will be most fruitful for their study.

Addressing Slow Trial Recruitment Throughout the Field

MJFF identified the easy-to-use action step for patients to connect to trials as the first critical need in addressing slow recruitment. Aiming to leverage advancements in technology to facilitate expedited recruitment, the foundation created Fox Trial Finder, a web tool that matches PD patients and control volunteers to research teams running open clinical trials.

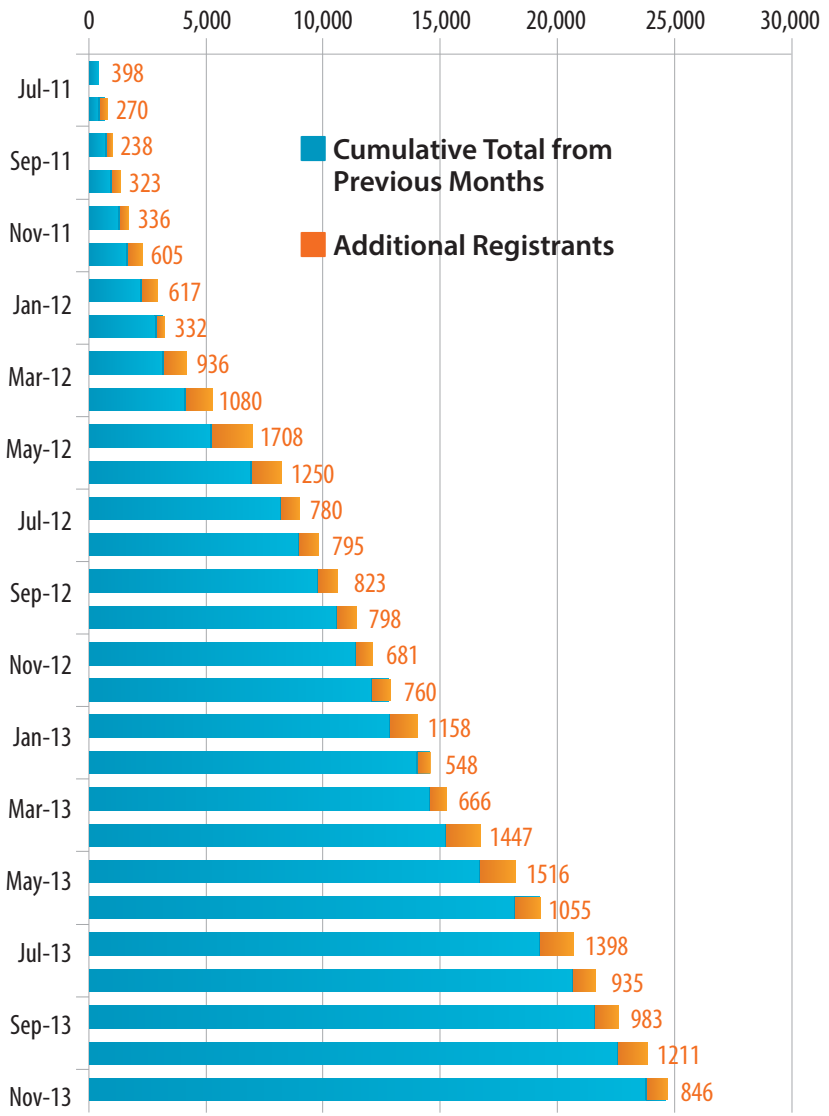
Here is how it works: PD patients and control volunteers visit www.foxtrialfinder.org to save a profile that includes their age, gender, location, date of diagnosis, disease progression, symptoms, treatment history, and knowledge of genetic mutations associated with PD. Simultaneously, the coordinators of trials that have been approved by the appropriate institutional review boards are invited to submit descriptions of their studies and the profile of the ideal subject they are looking for, based on study inclusion/exclusion criteria.

Volunteers and trial teams are matched to one another through the website's proprietary algorithm, which takes into account an individual's profile and the profile of the volunteer that each study is looking for. All matches are based on ZIP code, and made on an ongoing basis, so that when new trials are added to the website, volunteers receive automated e-mail alerts when a new trial matches their profile.

When a trial of interest is matched to a volunteer, or when a volunteer of interest matches to a trial, either the volunteer or the study team can review additional information about the match (volunteer profiles are always de-identified) and initiate a message to learn more and to explore trial enrollment offline.

Fox Trial Finder is currently available in English, French, Spanish, Italian, and German, and represents trials and volunteers from the United States, Canada, the United Kingdom, Australia, Ireland, Austria, Germany, Italy, France, and Spain.

FIGURE 1. Fox Trial Finder Registrations (From Launch Through November 20, 2013)



Clinical trial recruitment emerged as a priority over the last three to five years, as the understanding of the underlying biology and genetics of PD increased dramatically.

Launched in beta in July 2011 and officially in April 2012, Fox Trial Finder has amassed a database of more than 28,000 interested volunteers to date, and lists between 280 and 320 actively recruiting trials at any one time. Figure 1 indicates the growth in volunteer registrations through November 2013.

As of June 6, 2013, 466,979 matches had been generated between potential participants and recruiting trials, and 16,694 messages had been sent between interested potential participants and trial teams. A survey sent out to the database indicated that 38% of respondents have inquired about a specific trial and 11% have enrolled in a clinical trial using Fox Trial Finder.

Trial teams using Fox Trial Finder as a recruitment tool report accelerated recruitment timelines. From the patient perspective, Fox Trial Finder is a "one-stop shop" to learn about PD trials they may qualify for that are currently recruiting or are soon to begin recruiting, and to identify and connect with sites in their area that are recruiting subjects.

What More is Needed?

Launching Fox Trial Finder is not a complete solution. It might suffice for the first 10,000 to 15,000 volunteers, but for most of the 5 million PD patients worldwide, more is needed.

Since the launch, staff activities have focused on awareness building and education about the need for trial participants, beginning with our own e-mails, blog, newsletters, social media, and events. These foundation communications have focused on the need for recruiting volunteers, demystifying key myths about study participation, and sharing profiles of study volunteers with others. Also, a group of more than 150 Fox Trial Finder ambassadors has formed to empower champions of the site to make presentations and disseminate information about it.

Next, an extensive suite of materials was created to support outreach initiated by the foundation, patient ambassadors, trial sites, and others. Additionally, a new event series called Clinical Trial Fairs has been launched, bringing the concept of job fairs to clinical trials by inviting patients to browse tables hosted by local sites and adding an education symposium to demystify what is involved, what regulatory protections exist, what the consent process entails, and more.

From the three fairs that occurred in San Francisco, New York City, and Chicago, trial sites left the fairs with a combined 1,059 people to contact about participating in their studies (see Table 1 for additional details). Finally, a partnership among 16 other regional, national, and international PD organizations was formed to raise awareness about the need for participants and to educate about trial participation. Importantly, this group has agreed to share one consistent message and suite of materials about trial participation, driving people to Fox Trial Finder as a next step.

All of this is contributing to an ever-growing mass of volunteers who are educated about participation, well characterized in a database, and who can be relied upon by the field over time to participate in studies.

Of course, Fox Trial Finder only facilitates matching people to trials; actually enrolling them requires much more, including many offline activities funded, planned, and initiated by study sites and sponsors.

From Recruitment to Enrollment

Of course, Fox Trial Finder only facilitates matching people to trials; actually enrolling them requires much more, including many offline activities funded, planned, and initiated by study sites and sponsors. Acknowledging the need to address this issue from all sides, the foundation also built a new team to support these key stakeholders in their recruitment activities.

The signature program of the site- and sponsor-oriented activities is recruitment planning support provided to all foundation-funded and sponsored studies. This offering requires all of the foundation's awardees to plan for recruitment as they are applying for funding, to work with the team to refine their plan and budget accordingly upon study initiation, and to participate in regular recruitment update calls throughout the life of their grant.

Over time, these activities have enabled the foundation not only to help the actual studies with which it is working, but to become a long-term resource for recruitment knowhow in the PD field. This makes it possible for the next study trying to recruit a specific target or include a nontraditional procedure to leverage the lessons learned from a past study that faced a similar challenge.

Lessons Learned

From these activities, many key insights have emerged. First, planning ahead works. As evidenced by the decrease in the number of studies that have required "rescue" strategies, thoughtfulness about tactics and budgeting up front for recruitment plans have benefited recruitment timelines. Tailored, multipronged, phased strategies also seem to be the most successful. Working with sites to think hard about where they are going to find their target patient and sharing lessons learned from other trials have been most helpful.

Also, ensuring several tiers of plans has equipped trial managers with a long list of quality approaches to pilot and expand (or pilot and discontinue), depending on how well they work. Marketing assistance has helped study leaders think about crafting materials to inform patients about studies and cultivate them along the way.

Many studies provide an entire list of inclusion/exclusion criteria on recruitment materials, which can be overwhelming for patients. Others fail to explain the goal and scientific rationale for the study, skipping over information of primary interest to potential subjects and oftentimes the key motivator for participation. Information about a trial opportunity must be provided in a clear and concise manner, and patients need to understand trial goals and requirements for participation.

Helping the research team think about how to present complicated science simply and reformulate study communications has been beneficial. Finally, working with sites on strategies to convert qualified leads has been important. The leaky pipe metaphor highlights the role a site and sponsor can play in identifying "leaks" (i.e., why and where a subject will opt out of the enrollment process).[3]

Addressing issues related to the logistics and activities of a trial that could be valid reasons a subject may decline participation is a key recruitment planning activity that is often overlooked in planning, and sometimes ignored even once the trial is under way. Factors such as transportation, time required for participation, and reimbursement are valid and real day-to-day concerns for potential trial volunteers. Ensuring that trials have an adequate budget to provide parking or transportation service, have flexible operating hours, and can provide some reimbursement for patient time are simple fixes to these types of "leaks."

TABLE 1. Clinical Trial Fair Outcomes Across Three Markets: Chicago, New York, and San Francisco.*

Clinical Trial Fair	Participating Research Institutions	Clinical Trials Exhibited	Guests Attended	Leads Generated	Screening Visits	Enrolled Subjects
Chicago 9/7/2013	4	24	210	89	7	2
New York City 10/19/2013	12	43	330	745	164	68
San Francisco 12/14/2013	5	24	310	334	87	16
TOTAL	21	91	850	1168	258	86

**Due to the recency of these events, numbers provided only represent data collected to date. Contact the lead author for updated numbers.*

Other conversion issues may arise due to a daunting or difficult procedure included in a trial. In one ongoing study requiring seven spinal taps, significant planning and site support were provided to address this procedure: Principal investigator and coordinator talking points were developed; observation of the procedure with experienced colleagues was planned for; and a patient handout and video were created to explain the procedure. Although most sites had an early learning curve, all of them became experts at speaking to patients about this, so much so that the spinal tap is almost never cited as a reason for turning down enrollment in the study. Further, continued willingness to complete this procedure has sustained, with more than 90% of visits that were expected to involve a spinal tap being successfully completed.[5]

Resources and Further Considerations

MJFF's experience advising studies on these tactics over the last two years has resulted in an ever-evolving document tracking all of the best practices that have been successful. This document is currently offered as a resource to potential grantees to begin their recruitment planning, and is posted on the foundation's website for anyone in the field to consult during their recruitment planning activities. Additional handouts on specific procedures and research needs have also been developed and posted for the field to use (at www.michaeljfox.org/focusonclinicaltrialrecruitment).

The activities the foundation has initiated to date are a start to addressing these issues for the field. With the launch of one project that addresses one piece of the challenge of recruitment, other new objectives that need to be addressed are emerging. The foundation team working in this area continues to amass a list of new initiatives and ideas, and is prioritizing opportunities as human resources allow.

Future anticipated activities include developing a PD coordinator community to share materials, ideas, and lessons learned from recruitment, and assembling an online recruitment toolkit that supports materials creation and messaging for all studies. On Fox Trial Finder, planned developments include making available a study feasibility analysis tool so investigators can search the database as they are designing a protocol to assess the "recruitability" of the study; lay-friendly editions of study results for the patient community; and improved analytics for trial teams. Physician outreach and education are other major opportunities for increasing volunteer registrations on the site.

Conclusion

We have discussed the strategy development and experience of one disease advocacy organization. We hope that this experience serves as an example for other players involved in drug development to consider opportunities to innovate and create novel partnerships for addressing the roadblock of recruitment for trials systematically.

For site investigators or coordinators, this may mean thinking creatively about recruitment for the next trial and asking the study sponsor for funding to implement novel ideas. For sponsors, it is an opportunity to think broadly and be inventive about how to plan recruitment for the next study. For other disease advocacy organizations, determining if staff can devote some of their time to these activities may be possible.

Considering all of the activities involved in truly functioning as a "department of cures" is a daunting task, and perhaps no one player—MJFF included—may ever fully realize the myriad of functions that serving that role requires. However, acknowledging that we all play a part in moving new therapies through the drug development process, and that this goal is a shared one, can be a pathway to new ways of thinking.

Disruptive innovation, creative partnerships, and a willingness to invest resources to bolster the field have contributed to the early successes in this arena for the foundation's programs. Over time, the goal is to move the dial on the number of subjects enrolled per month and, eventually, to see recruitment rates increase exponentially.

Imagine a world where having to worry about the expense it takes to recruit is eliminated, because all of the people you need are registered and well classified already. Perhaps it would be possible to cut the recruitment period in half in such a world. What if the rate-limiting step for trial enrollment was a site's capacity to schedule visits and consent people?

At MJFF, we believe that all of these aspirations are possible if those who are engaged in disease research are empowered to think strategically for the field, take calculated risks to invest, pilot new ideas, and replicate success broadly for clinical trial recruitment. In fact, this is an approach that can be applied to anything else that may stand in the way of getting new therapies to pharmacy shelves for patients and of making much-needed research progress in the field.

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Opportunities to Optimize Study Design to Drive Development Performance and Efficiency

PEER REVIEWED | Kenneth A. Getz, MBA

[DOI: 10.14524/CR-13-00062R1.1]

LEARNING OBJECTIVE
After reading this article, participants should be able to characterize protocol design practices, the ways that complexity has increased over time, and new approaches to improve study design.

DISCLOSURES
Kenneth A. Getz, MBA: Nothing to disclose.

During this past decade, a growing body of research in the literature has revealed a sobering trend demanding remediation: Study design complexity across a variety of parameters, including the number of protocol endpoints and objectives and the number of volunteer eligibility requirements, have been rising steadily—with no end in sight. Research has also demonstrated that study design complexity adversely affects clinical trial performance, cost, and efficiency, suggesting that study design optimization holds the key to addressing the perennial industry challenges of rising cost, development risk, and cycle time. This article summarizes the trends in protocol design practices, their effects on drug development performance, and the steps that sponsor organizations are taking to streamline and improve study design.

Trends in Study Design Practices

Research conducted by the Tufts Center for the Study of Drug Development (CSDD) has captured remarkable growth in study design complexity—both scientifically and operationally. Table 1 shows the increase in seven different factors for a typical Phase III protocol in 2002 as compared to one in 2012.[1,2]

Rising study design complexity is inevitable. New scientific knowledge about chronic disease mechanisms and how to measure their progression and economic impact requires more elaborate and robust ways to demonstrate drug safety, efficacy, outcomes, and comparative effectiveness. Crowded classes of investigational therapies and the ongoing movement to develop personalized medicines are pushing research sponsors to collect more data and to target smaller patient subgroups to more effectively differentiate small and large molecule interventions.

Research sponsors are collecting an ever wider array of data, including biomarker, genetic, outcomes, economic, and companion diagnostic data, which may be analyzed as part of the study or stored and analyzed at a future date. Meanwhile, medical scientists and statisticians often add procedures to gather more contextual data to aid in their interpretation of the findings and to guide development decisions. These procedures may provide clinical validation and help explain unusual and unexpected results.

However, there is no question that rising study design complexity is also a function of risk management, risk avoidance, and outdated practices. Drug developers routinely add procedures guided by the notion that the marginal cost of doing so, relative to the entire clinical study budget, is small when the risk of not doing so is high.

Additional procedures are performed as an insurance policy against the study failing to meet its primary and key secondary objectives. The data from these procedures may prove valuable in *post hoc* analyses that reveal new and useful information about the progression of disease, its treatment, and new directions for future development activity.

Also, clinical research teams add procedures for fear that they may neglect to collect data requested by regulatory agencies and health

TABLE 1. The "Typical" Phase III Protocol in 2002 and 2012

	2002	2012
Total Number of Endpoints	7	13
Total Number of Procedures	106	167
Total Number of Eligibility Criteria	31	50
Total Number of Countries	11	34
Total Number of Investigative Sites	124	196
Total Number of Patients Randomized	729	597
Total Number of Data Points Collected*	N/A	929,203

*Source: Tufts CSDD; *Medidata*

authorities, purchasers, and payers. Failure to do so could potentially delay regulatory submission, product launch, and product adoption. As well, medical writers and protocol authors often permit outdated and unnecessary procedures into new study designs because they are routinely included in legacy protocol-authoring templates and operating policies.

The Impact of Study Design Complexity on Performance

Research published in peer-reviewed and trade journals indicates that higher levels of study design complexity are associated with lower levels of clinical research data quality and higher study costs. Friedman and colleagues found, for example, that the high volume of data collected in today's studies distracts research scientists, compromises the data analysis process, and ultimately harms data quality.[3]

As more data are collected during protocol administration, error rates increase, according to Nahm et al.[4] Barrett found that more procedures per protocol were associated with a higher incidence of unused data in New Drug Application submissions to the U.S. Food and Drug Administration.[5] Abrams et al. found that unused clinical data compromise the data analysis process.[6]

Higher levels of study design complexity are also associated with longer cycle times and with lower patient recruitment and retention rates.[7] Clark found, for example, that the collection of excessive and unnecessary clinical data drives longer study durations. The author warned that data collection and regulatory agency submission delays may ultimately harm regulatory approval rates.[8]

A comprehensive analysis of peer-reviewed academic studies by Ross and colleagues found that health professionals were less likely to refer patients to, and patients were less likely to participate in, more complex clinical trials.[9] Madsen showed that patients are significantly less likely to sign the informed consent form when facing a more demanding protocol design.[10]

Further, Boericke and Gwinn found that the higher the number of study eligibility criteria, the more frequent and longer were the delays in completing clinical studies.[11] Also, Andersen and colleagues showed that volunteer dropout rates are much higher among patients participating in more complex clinical trials;[12] the authors cautioned that, when volunteers terminate their participation early and are lost to follow-up, the validity of the study results may be compromised.

More Insights on the Costs of Complexity

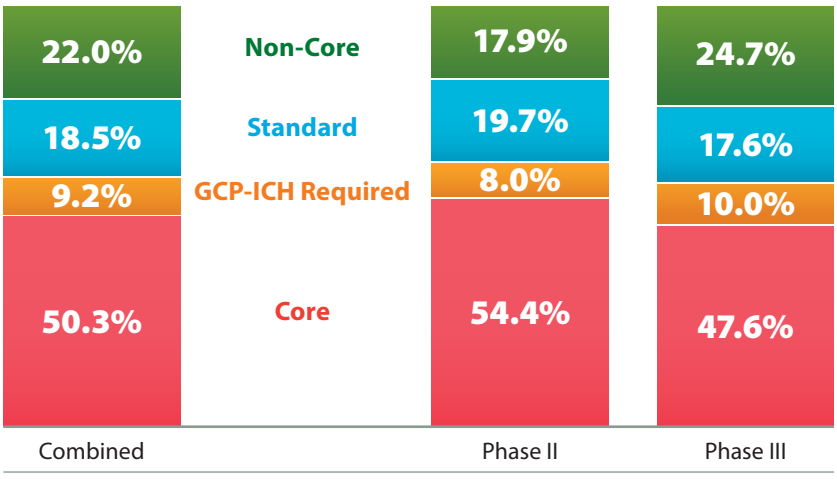
Tufts CSDD research has shown that complex protocols are inversely related to recruitment and retention effectiveness and study cycle time.[7] Our research has also found that more complex protocols are associated with a significantly higher number of protocol amendments.

Our analysis of more than 3,400 protocols found that complex protocols are amended nearly twice as often (an average of 2.3 times), cost more than $1 million, and take four additional months to implement. Clearly, protocol amendments are highly disruptive, causing significant unplanned expense and delays for research sponsors and unexpected burden for investigative sites.

In June 2013, Tufts CSDD published the results of a study demonstrating that, whereas the marginal cost of adding a protocol procedure may be low relative to the overall study budget, in the aggregate, spending on less essential, non–mission-critical protocol procedures is substantial. Of the 25,103 individual Phase II and III protocol procedures analyzed in the study, more than one out of five procedures (22%) supported tertiary and exploratory objectives and endpoints (see Figure 1). The proportion of procedures collecting "non-core" data in Phase III studies alone was even higher (25%). The average cost to administer procedures supporting these non-core objectives and endpoints represented 19% ($1.7 million) per Phase III study budget and 13% ($0.3 million) per Phase II study budget.[2]

A number of sponsor organizations have solicited feedback from principal investigators, study coordinators, and patients to identify areas where study design feasibility can be improved prior to final approval of the protocol.

FIGURE 1. Distribution of Protocol Procedures by Endpoint Type



Source: Tufts CSDD 2013 analysis of 25,103 Protocol Procedures

The total cost to the pharmaceutical industry each year to perform procedures supporting non-core objectives and endpoints for all Phase II and III protocols is an estimated $4 to $6 billion (U.S.). This estimate is very conservative, as it excludes all indirect costs for personnel and infrastructure required to capture, monitor, clean, analyze, manage, and store extraneous protocol data, and it does not include the cost of unnecessary risk to which patients may be exposed.

Optimizing Study Design

During the past several years, study design complexity has not escaped the attention of sponsor companies, and researchers at a growing number of organizations have taken steps to evaluate their protocol design practices and compare them to industry benchmarks.

Sponsor organizations have referred to published data in peer-reviewed papers authored by Tufts CSDD and others to compare internal study design practices to benchmarks. Commercially available software and consulting services are also available to assist sponsor companies in diagnosing problems and implementing new practices to streamline and simplify study design.

In addition to devoting time and resources to diagnose the problem, sponsor organizations are looking for ways to operationalize higher levels of protocol feasibility. Whereas scientific objectives trumped all else in the past, operating objectives now carry substantially more weight.

A number of sponsor organizations have solicited feedback from principal investigators, study coordinators, and patients to identify areas where study design feasibility can be improved prior to final approval of the protocol. Feedback mechanisms are conducted as in-person meetings and focus groups; others are conducted online using social and digital media communities. Transparency Life Sciences, Genentech/Roche, and Novartis are examples of sponsor organizations—both small and large—that are using panels of investigators, coordinators, and patients to provide feedback.

Sponsors and contract research organizations (CROs) are also revamping their protocol authoring practices. To that end, a new reference was made available in early 2013 for protocol authors called SPIRIT, through an initiative designed to ensure that the purpose of protocol procedures are transparent and tied to core objectives and endpoints.

> Drug developers routinely add procedures guided by the notion that the marginal cost of doing so, relative to the entire clinical study budget, is small when the risk of not doing so is high.

SPIRIT checklists and guidelines were developed with input from 115 global, multidisciplinary contributors from the realms of medical writers, journal editors, regulatory agency staff, ethics committee members, and clinical research and healthcare professionals.

SPIRIT 2013 calls for simple, minimalist designs tied directly to the core endpoints and objectives defined by the clinical study report. It provides formatting conventions for various protocol elements (e.g., table of contents, glossary of terms, abbreviated terms), and its pilot-tested checklist can be downloaded for free.[14]

Meanwhile, half of the top 30 major pharmaceutical companies have established internal governance committees charged with challenging clinical teams to improve protocol feasibility, according to Tufts CSDD.[1] The creation of these committees within the past few years signals a growing commitment among major pharmaceutical companies to adopt a more systematic and long-term approach to optimizing study design. Committees are positioned within their respective organizations as objective governance and assessment mechanisms, offering guidance and input into the existing protocol review process without requiring organizations to alter legacy study design practices and procedures.

The committees raise clinical team awareness of the effects that design decisions have on study budgets and study execution feasibility. Typically providing input into the study design just prior to final protocol approval, committee members routinely offer insight into how protocol designs can be streamlined and better "fit to purpose." Ultimately, internal facilitation committees may drive long-term change in study design practices.

Another tactic, adaptive trial design, is one optimization opportunity that has received scant attention to date. Adaptive trial designs are preplanned, typically through the use of trial simulations and scenario planning where one or more specified clinical trial design elements are modified and adjusted while the trial is under way, based on an analysis of interim data.

Approximately one out of five (20%) late-stage clinical trials are using simple adaptive design approaches. A much lower percentage (< 5%) is using more sophisticated adaptations. Sponsor companies report that they expect the adoption of adaptive trial designs in earlier exploratory phase clinical trials to increase significantly within the next several years.[15]

Half of the top 30 major pharmaceutical companies have established internal governance committees charged with challenging clinical teams to improve protocol feasibility.

"Study terminations due to futility," the most common simple adaptive design used, is becoming the most widely adopted approach. Sponsor companies have found that early terminations due to futility are relatively easy to implement and should become standard practice in Phase II and Phase III studies across all therapeutic areas. A growing number of companies also view sample size reestimation as a relatively simple adaptive design to implement.

Although pharmaceutical and biotechnology companies have discussed and explored the concept of adaptive trial designs for decades, adoption has been slow for a variety of reasons. Internal organizational resistance appears to be the primary factor limiting more widespread adoption. Regulatory agency receptivity to the use of adaptive trial designs does not appear to be a barrier to adoption, though agency clarity with regard to its position on the use of adaptive designs appears to be lacking.

Clinical teams and operating functions perceive enrollment and logistical factors—specifically, delays and disruptions to trial execution, patient participation, and the distribution of clinical supplies—as major barriers to adoption. Sponsors are also concerned about:

- introducing bias following interim analyses;
- the lack of adaptive trial design experience among both internal development teams and CROs;
- gaps in infrastructure and technology to implement more sophisticated adaptive designs; and
- the limited capacity of independent data-monitoring committees.[15]

In the immediate term, adaptive trial designs are offering crossfunctional teams direct insights into study design through scenario planning and trial simulation prior to finalizing the protocol. Rigorous upfront planning—similar to optimization practices for traditional study designs—is forcing organizations to challenge protocol feasibility prior to placing the protocol in the clinic.

Closing Thoughts

The clinical research enterprise will look back on the current decade as the one in which protocol design optimization was the biggest focus. Facing a very challenging operating environment, protocol design holds the key to fundamentally and sustainably transforming drug development performance, cost, and success rates.

Study designs are already hyper-complex, and we can expect new areas in the future where preapproval clinical data will need to be collected to satisfy regulatory, point-of-care, and payer requirements. Out of necessity, given the high risk and limited returns of new molecular and biologic entities moving through the development pipeline, study design optimization is essential to driving substantially higher levels of drug development performance and efficiency.

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HOME STUDY TEST

New Insights into Study Volunteer Perceptions and Experiences to Inform Patient-Centric Clinical Trials

1. What percentage of the overall global public say that they do not trust research sponsors to inform them of safety concerns?

A. 5%
B. 28%
C. 51%
D. 73%

2. What proportion of the overall global public consider their general knowledge about clinical research to be well informed?

A. 20%
B. 33%
C. 75%
D. 81%

3. What is the top perceived benefit of participation in clinical research among the global public?

A. Helping to advance science
B. Improving patients' lives
C. Receiving monetary compensation
D. Receiving quality medical care

4. What is the top perceived risk of participation among the global public?

A. The risk to one's overall health
B. The risk of privacy violations
C. The risk of side effects
D. The risk of receiving a placebo

5. Compared to other age groups, 18- to 34-year-olds are:

A. the most willing to participate in clinical research studies.
B. equally willing to participate as other age groups.
C. slightly more willing to participate than other age groups.
D. the least willing to participate.

6. Which of the following is the top preferred source by the global public for information about clinical research?

A. The Internet
B. Retail pharmacists
C. Primary care physicians
D. Research center staff

7. What percentage of the global public has used social media to learn about clinical research?

A. 25%
B. 40%
C. 60%
D. 80%

8. What percentage of global study volunteers rate receiving the results of their clinical trial as a top factor influencing their decision to participate?

A. 19%
B. 45%
C. 62%
D. 71%

9. At the completion of a clinical trial, 95% of global study volunteers say that they would participate again. Compared to past surveys, this percentage has:

A. increased by 10 percentage points.
B. increased by 30 percentage points.
C. decreased by 5 percentage points.
D. decreased by 25 percentage points.

10. Of those patients deemed ineligible to participate after the prescreening, what fraction choose to discontinue looking for a relevant clinical trial?

A. One-third
B. Two-thirds
C. One-fourth
D. Three-fourths

Accelerating Drug Development for the Field: Building Clinical Trial Recruitment Infrastructure in Parkinson's

11. What is the average amount by which a study enrollment period is extended in central nervous system diseases?

A. 50%
B. 79%
C. 116%
D. 157%

12. What is the average enrollment rate (subjects per site per month) in trials in central nervous system diseases?

A. 0.5 subject per site per month
B. 0.85 subject per site per month
C. 1 subject per site per month
D. 1.3 subjects per site per month

13. According to MJFF's survey of Parkinson's patients, what percentage of respondents were at least somewhat likely to be willing to participate in a trial?

A. Less than 20%
B. 47%
C. 68%
D. More than 80%

14. What are three common myths about what is involved in trial participation?

1. Trials require taking a drug or using a new device.
2. Participants will undergo procedures to which they did not agree.
3. Trials will interfere with a participant's routine clinical care.
4. Patients will receive less attention in their clinical care as a result of their trial participation.

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

Any revisions to the questions that occur after the issue is published will be included in the online test located at www.acrpnet.org under Professional Development: Home Study.

15. What is the ideal time for a study to develop a recruitment strategy?

A. When recruitment starts to slow down
B. When the study starts
C. When half of the sites have been activated
D. When all of the sites have been activated

16. The development of a recruitment plan should be led by:

A. the study sponsor.
B. each site to determine what is best for them.
C. the site of the overall study principal investigator.
D. a group of sites that are most successful at recruitment.

17. Recruitment plans should include which of the following?

1. Money to support recruitment tactics
2. Strategies to identify qualified individuals to approach about participating
3. Standard operating guidelines on how procedures should be conducted
4. Materials and instruction on how to convert qualified leads

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

18. What are three barriers to clinical trial recruitment?

1. Lack of patient interest in participating in trials
2. Lack of patient knowledge about trial opportunities in their area
3. Lack of patient awareness about the need for trial volunteers
4. Lack of funding to support participant travel and accommodation in trials

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

19. What are three key reasons identified in the article for why a qualified person may not participate in a trial?

1. It is too costly for the person to travel to the trial site.
2. The person doesn't want to participate in observational research.
3. The person is scared of daunting procedures in the study.
4. The person's schedule doesn't allow for visits to the site during work hours.

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

20. Which of the following are key tactics to support recruitment discussed in the article?

1. Handing out flyers at a pharmacy
2. A clinical trial matching tool
3. A toolkit of materials to support recruitment at sites
4. A job fair-like "clinical trial fair"

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

Opportunities to Optimize Study Design to Drive Development Performance and Efficiency

21. A typical Phase III protocol in 2012 had how many average procedures and eligibility criteria?

A. 58 procedures; 6 eligibility criteria
B. 101 procedures; 10 eligibility criteria
C. 170 procedures; 11 eligibility criteria
D. 250 procedures; 5 eligibility criteria

22. In how many countries and investigative sites was the typical Phase III protocol in 2012?

A. 11 countries; 129 investigative sites
B. 26 countries; 176 investigative sites
C. 34 countries, 196 investigative sites
D. 82 countries; 385 investigative sites

23. How many average eligibility criteria did the typical Phase III protocol have in 2012?

A. 20
B. 35
C. 50
D. 80

24. Higher levels of study design complexity are associated with:

A. lower levels of data quality; higher costs; longer cycle times.
B. lower levels of data quality; lower costs; longer cycle times.
C. higher levels of data quality; higher costs; longer cycle times.
D. higher levels of data quality; higher costs; shorter cycle times.

25. What is the estimated cost to implement an amendment for a complex protocol?

A. $500,000 and one-month time delay
B. $1 million and one-month time delay
C. $500,000 and four-month time delay
D. $1 million and four-month time delay

26. What percent of Phase III procedures performed per protocol support noncore endpoints and objectives?

A. 25%
B. 33%
C. 40%
D. 75%

27. What was the estimated total cost to perform noncore procedures supporting all active Phase II and III clinical trials this past year?

A. US $250-$500 million
B. US $500-$750 million
C. US $1-$2 billion
D. US $4-$6 billion

28. New approaches to soliciting patient and study staff input into protocol feasibility include:

A. protocol authoring tools.
B. interacting via social media.
C. linking procedures to protocol endpoints.
D. new governance committees.

29. What percentage of sponsor companies have established formal governance mechanisms to challenge protocol feasibility?

A. 25%
B. 33%
C. 50%
D. 67%

30. What is the most common adaptive trial design used?

A. Seamless Phase II-III studies
B. Early termination due to futility
C. Sample size reestimation
D. Dose response assessment

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Sponsor-Investigators, Approval Stamps, and Repeat Subjects

Q. Is the investigator responsible for monitoring a clinical study, even at his or her own study site, when serving as a "sponsor-investigator" for a study?

When an investigator agrees to conduct an investigator-initiated research project, he or she assumes all the responsibilities and must fulfill all the regulatory requirements facing both the study sponsor and the clinical investigator.

A. When an investigator agrees to conduct an investigator-initiated research project, he or she assumes all the responsibilities and must fulfill all the regulatory requirements facing both the study sponsor and the clinical investigator. As a sponsor-investigator, an investigator must provide for the monitoring at his/her own study site and any other sites included in the study.

Even if it's just the investigator's own site that is involved in the study, the sponsor-investigator still needs a clinical monitor to review the data and the study conduct. That does not necessarily mean the investigator has to hire a monitor; he/she just needs to make sure that that person is qualified to do monitoring, knows what to do, and actually does monitor the study.

I've sometimes seen sponsor-investigators, if they are in a large hospital, use members of the institutional review board (IRB) or staff from the clinical trials office to go in and review these types of studies. At any rate, under the Food and Drug Administration's (FDA's) investigational new drug regulations, even the sponsor-investigator needs to show that the study has been monitored (CFR 312.56(a) in the *Code of Federal Regulations*).

The latest version of the FDA *Compliance Program Guidance Manual* 7348.811 (December 2008) specifically asks its field staff, in inspecting sponsor-investigators, to "determine if any monitoring was done for the study, and if so, describe. Obtain a copy of the monitoring [standard operating procedure], if available." Citations for sponsor-investigator failures to provide for clinical monitoring appear in recent FDA Warning Letters as well.

Finally, the Center for Biologics Evaluation and Research (CBER) compliance officials have indicated their intent to focus more closely on sponsor-investigator studies. The specific concern has related to the fact that CBER oversees many such studies, and more specifically to the fact that the center is interested in assessing how clinical investigators are monitoring these trials.

In March 2013, ACRP and the Investigator Initiated Sponsored Research Association (IISRA) announced the initiation of a strategic partnership, which culminated in fall 2013 with a full merger of IISRA with ACRP. This group has published several guidelines and position papers on practices for the conduct of investigator-initiated research. Visit www.acrpnet.org/Interest-Groups/Investigator-Research.aspx for more information on this affiliation and links to the shared resources.

Q. My site works with a number of different central IRBs. Some place an approved stamp on the informed consent form and others do not. Is an approval stamp from the IRB required on an informed consent form?

A. Although it is common practice for some IRBs to place a stamp on the informed consent form, either on the cover page or on every page indicating that the form is "IRB approved," this is not required by regulation. Some IRBs do not do this, and rely instead on the date and version control by the submitter to know which version is the most current approved version.

Some question has been raised that such a stamp on the informed consent form might cause a potential subject to believe that IRB approval implies the study is safe, or could otherwise be misinterpreted by a potential subject as an endorsement of the trial. In response to a question about the use of a stamp in 2006, the FDA indicated that it did not have a problem with the use of an approval stamp by an IRB to indicate that the form is approved and current.

Interestingly, in several Warning Letters to IRBs over the years, the FDA has actually suggested the IRB adopt the use of a stamp to assure that the most current version is used. In one Warning Letter, the FDA indicated that, "This is not required by regulation, but it is considered to be a good practice."

FDA has reiterated that an approval stamp is not required by regulation. The International Conference on Harmonization's Good Clinical Practice Guideline also specifies only that there be documented approval by the IRB or ethics committee (EC), but provides no mention that the IRB/EC should stamp the consent form itself.

Do you have a Good Clinical Practice question or an issue that has come up at your site or company? If you are not sure of how to proceed, please send an e-mail to gcp@moriahconsultants.com, and I will answer it in an upcoming column.

Q. My site conducts many Phase I studies using healthy volunteers. Are there any FDA requirements or standards establishing the length of time a study participant must wait after finishing one drug study before beginning the screening process for another drug study?

A. FDA regulations do not specify a timeframe that should elapse between a subject's enrollment in two successive trials. The agency has consistently stressed that there be an adequate washout and recovery period to ensure that subjects are appropriately protected and risks are minimized.

On the other hand, sponsors often require that study subjects not have participated in other clinical trials for some specific period prior to enrollment in their own trials (for example, a 30-day washout period), and usually spell this out in the study protocol. This may vary depending on the sponsor and properties of the investigational product, since there are some examples of drugs with a long half-life (the time it takes for the drug to clear from the circulation) that necessitates a much longer interval between studies.

Thus, although a 30-day washout is a common criterion, many study protocols specify a longer time period (60 or 90 days). To determine an appropriate interval, information about the pharmacokinetics (e.g., absorption, dissolution, metabolism, excretion) of the drug needs to be considered.

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Connecting the Right Sites to Promising Trials:

The Role of Web-Based Feasibility Assessment

PEER REVIEWED | Gustavo Luiz Ferreira Kesselring, MD | Gerd Brunner, MD, PhD | Juan Luis Yrivarren, MD | James Rosenstein | Fabio Thiers, MD, PhD

[DOI: 10.14524/CR-13-00055R1.1]

The fact that clinical trial planning bottlenecks have become a significant burden for the pharmaceutical industry is well-known. The number of New Drug Application approvals by the U.S. Food and Drug Administration is declining, despite greatly increased research and development (R&D) spending. A large number of subjects need to be recruited in a timely fashion, and there are growing pressures for time and cost containment. Time to market is critical, and any delay in a clinical drug development program will diminish the market value of a drug.

The "fear" of a delay constitutes an immense driving force in the process of site selection. In a study of several hundred global clinical trials, sponsors found out that 11% of sites, on average, in any multicenter clinical trial will fail to enroll a single patient, and 39% will under enroll.[1] This is testimony to the fact that the site selection process is still painfully broken, despite the overwhelming available information about the inefficiencies incurred through the existing processes.

This article examines the root causes behind the inefficiencies in site selection and engagement, and presents available and promising solutions to the problem, with specific emphasis on web-based tools, including in particular online feasibility assessment.

Background

Selection of the right sites for a promising clinical trial is clearly the most relevant step in the planning process for subsequent successful study conduct. Many obstacles stand in the way of efficient implementation of this process, and the figures speak for themselves:

- Today, developing a drug can cost more than US $1 billion, and a single clinical trial can cost more than US $100 million.
- Between 50% and 60% of research sites enroll fewer than two patients in their studies,[2] and about 80% of clinical trials are delayed[3] because of unfulfilled enrollment.
- An estimated US $10 billion a year is wasted because of poor site selection,[4] which is due to a failure to match trial planners with appropriate, efficient research sites.
- In the case of oncology, less than 5% of patients currently participate in clinical trials.[5] If 10% participated, studies could be completed in a significantly shorter period instead of the current three to five years.[5]

Thus, poor site engagement is an impediment to medical innovation. A new approach is needed. Proper planning of clinical trials is key to the success and efficient use of R&D investments so that new therapies can reach patients.

The Causes of Site Selection Inefficiencies

Pharmaceutical Company Practice

Although sponsors are aware of the need to change the established way of preparing and conducting clinical trials, they have been thwarted by the lack of appropriate tools and approaches to follow up on this insight.

In their article, "Fixing the Protocol Feasibility Process,"[6] Beth Harper and Nikki Christison summarize the root causes of poor site selection: "Assessment teams are often given unrealistic timelines, use tools they know to be ineffective, and follow inefficient processes they know prevent them from doing their work properly."

Site selection is very often influenced by a variety of complicated considerations. Sponsors appear to believe at times that the more key opinion leaders for the given indication are involved in a clinical trial, the better it is for the trial; but are key opinion leaders or the best prescribers of drugs always the best investigators? Daily experience very often reveals the opposite, and the following example clearly indicates what is involved.

During a site selection visit for an international diabetes trial, one of the authors of this article witnessed the coordinating investigator for the trial, a key opinion leader who was chosen by the sponsor, telling the project leader directly: "But you have to know that I do not feel confident about the comparator that is used." Given the obstacle created by the opinion leader's obstinacy, this site enrolled only three patients. Two patients were screening failures and the remaining patient withdrew from further participation after several weeks. The site enrolled no further patients through the end of the study, although several other sites enrolled more than 15 patients each in the same period.

For the performance of a site in a clinical trial, the number of publications of the investigator is not a truly hard parameter. The setup of a site and its performance in previous trials (e.g., recruitment capabilities) are much more important for the success of a trial. However, when selecting sites for a new trial, sponsors often do not take these crucial parameters into account. They tend to place trust in unreliable and/or outdated information, or the site selection is often influenced by personal and marketing considerations.

A recent analysis by the Tufts Center for the Study of Drug Development (CSDD) involving 150 studies and nearly 16,000 trial sites revealed that 90% of clinical trials meet their patient enrollment goals, but in many cases do so only by doubling their original enrollment timelines.[7]

Flawed site selection is not the only reason for this time-, money-, and resources-wasting reality. As mentioned above, 50% to 60% of research centers end up with fewer than two patients in any given trial, falling behind the recruitment expectations.[2] Tufts CSDD also found out that pharmaceutical companies and contract research organizations (CROs) rely very often on a limited number of traditional recruitment and retention tactics, and the same seems to apply for the identification and selection of trial sites.

Site-Related Issues

A number of factors behind these difficulties are directly related to the sites themselves. As explained by Kenneth A. Getz at Tufts CSDD: "The site landscape has been in a perpetually nascent and fragmented state." It is "a landscape that has been spinning its wheels for 30 years, unable to mature or achieve scale efficiency and operating sophistication."[1]

At the same time, given the global expansion of clinical trials, there are more than 400,000 disease-specific research sites worldwide in more than 59,000 institutions.[4] Trial planners simply do not have adequate analytics about investigators and their teams, research centers and the locations where they operate, the local number of enrolled and available patients, and regulatory timelines. Information is often inaccurate and outdated, or simply does not exist.

Moreover, this information disconnect has forced trial planners in pharmaceutical companies and CROs to compensate by overloading the centers with detailed requests for information (feasibility questionnaires), which can be voluminous (up to 40 pages) and often go unanswered. In addition, communication is inefficient during feasibility assessment; there is a lack of harmonized and integrated epidemiological and demographic data; and critical information about the highly complex, dynamic, and global regulatory environment is not easily accessible.

The big question is whether or not the feasibility and final site selection process leads to accurate knowledge of the site and its real capabilities with respect to patient recruitment. Questionnaires often need to be completed with very tight, unrealistic deadlines—perhaps even several times for the same trial when a number of CROs are involved. Information provided is taken at face value (or discounted using arbitrary "correction factors"); and the same sponsor commonly repeats information requests on general site capabilities in every questionnaire.

Online feasibility assessments consist of the efficient use of digital capabilities to enable sites to complete site assessments more quickly and with less effort.

More and more, the clinical research enterprise is moving in the direction of sharing data and fostering a more collaborative approach.

Furthermore, no information is given as to when and how the selection decision will be made. Since a large proportion of the questionnaires do not lead to site selection, the sites are seldom informed officially when rejected. For the few that are informed, there is no information on what criteria were used to make the decision.

This whole process leaves the sites in limbo, with uncertainty over whether a rejection was related to site capabilities, geographic distribution of the study, or simply cancellation of the program. It creates the impression that sites are commodities, with no sense of partnership and no learning takeaways to be gained through the feasibility process. Thus, sites struggle to communicate their capabilities to trial planning professionals globally. Moreover, they need to involve expensive staff to respond to the feasibilities, which turns into business in less than 5% of cases.[8]

The Way Forward

Is it so difficult to get reliable and up-to date information about professional and successful working trial sites worldwide? One of the main difficulties has been the absence of a structured venue for sharing information about sites, site investigators, and the environment in which they operate. However, there is increasing awareness of the potential of "Big Data." The tools of information technology can be put to good use to organize and share information, keep it up to date, and improve communication among all stakeholders toward the goal of streamlining trial planning processes.

Recent years have seen the development of new, innovative, and neutral tools for site selection that can significantly address the current dilemma. Deborah Borfitz, in an article in *Clinical Informatics News,*[9] presented several of these new tools, including:

- Citeline's Sitetrove, with profiles from a large number of investigators at many sites;
- BioPharm Clinical's Study Advisor, for timeline and enrollment forecasting;
- ViS' online feasibility platform; and
- IMS Health's SiteOptimizer, which uses history and predictive analytics to improve clinical trial enrollment.

For some companies, the primary goal goes beyond providing information about the most appropriate investigators and trial sites to sponsors/CROs. An online feasibility platform may, for example, focus also on the reduction of the administrative burden related to feasibility questionnaires for the sites, while facilitating personal contact between trial planners and research sites.

Online feasibility assessments consist of the efficient use of digital capabilities to enable sites to complete site assessments more quickly and with less effort. Sites can thus complete their profiles, answering more than 85% of the general and disease-specific questions raised in feasibility assessments, keep them up to date, and share them as many times and with as many sponsors/CROs as they want, for free. In turn, sponsors and CROs have free access to thousands of feasibility profiles at their fingertips.

Online feasibility assessment offers three main benefits for sites:

- Visibility—Site personnel are able to showcase their disease-specific capabilities and gain direct exposure to decision makers, therefore increasing revenue from more trial participation.
- Cost savings—Sites are able to reduce expenditure related to marketing and feasibility assessments, and reduce waste from inefficient communication.
- Communication—Site staff are able to efficiently exchange technical information with sponsors, CROs, and other sites, reducing duplication of efforts and starting trials that can bring in revenue more promptly.

The implications for sites are substantial. Site staff need to fully understand their capabilities and be willing to share this information transparently in a very comprehensive manner, in order to proactively promote their capabilities to sponsors. The current options are clear, in particular those who have a crowd-sourcing platform, where the sites provide comprehensive and standardized data. (Crowdsourcing is the practice of obtaining needed services, ideas, or content by soliciting contributions from a large group of people and especially from online communities, rather than from traditional employees or suppliers. In the case of an online feasibility platform, crowdsourcing means the possibility for research centers and other parties to provide structured data online, making it possible to efficiently aggregate and organize information and keep it up to date.)

The time has come for sites to take the front seat and actively help to change the current business model of passively waiting for questionnaires that have been shown to be irrelevant in improving the site selection process. If sites are successful in making this happen, then the sponsors will need to

show that they can use these data to select the right sites and accomplish their critical goal of getting medicines to market on time.

The industry as a whole is increasingly aware of these challenges and opportunities to make an impact. A number of initiatives address such inefficiencies, harmonize data, and streamline the clinical trial process. In particular, TransCelerate Biopharma Inc., created in 2012 by 10 leading pharmaceutical companies, has taken a number of significant steps, with initiatives related to site qualification and training and the establishment of a shared investigator portal.[10] The Alliance for Clinical Research Excellence and Safety (ACRES),[11] established to enhance safety, quality, and operational efficiency across the entire clinical research enterprise, supports the collection, sharing, and analysis of information.

Conclusion

Increasingly, the clinical research enterprise is moving in the direction of sharing data and fostering a more collaborative approach, a key aspect of which can be called "collaborative analytics."

Just as everybody is using new tools when buying a camera or a car, sponsors are beginning to do the same for the preparation of their trials and the selection of trial sites. Beyond the benefits to sites and sponsors, patients deserve a dramatic improvement in the whole operational model. Not only will they get breakthrough drugs sooner, with the promise of a more efficient development process, they will also have access to medical innovations at lower prices.

Despite the need for a fundamental paradigm shift, it will take significant investments of time and effort for all players to embrace new operational models. At the same time, people are quickly getting used to the now pervasive access to data and online communications. Technology platforms like Google maps, LinkedIn, and Bloomberg (in the financial industry) are now enabling all of us to quickly navigate complexity, find answers, and immediately connect with the people who can best perform a task. Such smart navigation and live connections are welcome innovations for the clinical research enterprise.

Clinical trial planning is one of the major bottlenecks in pharmaceutical drug development. Reliance on feasibility questionnaires has proven to be highly inefficient. New digital technologies, including an online feasibility platform, produce significant improvements in terms of efficient site selection, crucial cost reductions and time savings, and welcome access to new treatment possibilities for patients.

The time has come for sites to take the front seat and actively help to change the current business model of passively waiting for questionnaires that have been shown to be irrelevant in improving the site selection process.

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Brent A. Ibata, PhD, JD, MPH, RAC, CCRC

Compassionate and Emergency Use of Unapproved Drugs, Devices, and Biologics

For a patient with a serious life-threatening disease or condition, expanded access to an investigational product may offer an option when there are no satisfactory non-investigational alternatives.

Historically, an investigational drug, device, or biologic was available only through a clinical trial and then only for eligible patients. In the late 1980s, the U.S. Food and Drug Administration (FDA) began to publish regulatory changes to gradually expand access to investigational products for serious diseases. In 1997, this expanded access was extended to investigational devices and, in 2004, Congress added an emergency use provision to permit the broad use of unapproved products in the case of a national emergency.

Except for the emergency use of an investigational device to protect the life or physical well-being of a subject in an emergency, each of these expanded uses requires regulatory approval prior to the off-protocol use.

Regulatory History

In 1987, the FDA published a final rule that describes expanded treatment uses of investigational new drugs (INDs) outside clinical trials.[1] In 1997, the FDA amended the Investigational Device Exemption (IDE) regulations to allow for the treatment use of investigational devices beyond patients enrolled in a clinical trial.[2] That same year, Congress passed the FDA Modernization Act, which added specific provisions for expanded access to investigational drugs for treatment uses.[3] In 2009, the FDA published a final rule implementing the expanded access provisions.[4]

The institutional review board (IRB) regulations at 21 CFR Part 56 in the *Code of Federal Regulations* defines "emergency use" to mean "the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval."[5] This "emergency use" of a test article is exempt from prior IRB review, "provided that such emergency use is reported to the IRB within 5 working days."[6]

The Federal Food, Drug, and Cosmetic Act permits the authorization for shipment of "investigational drugs or investigational devices for the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations."[7] The criteria for compassionate or emergency use of an unapproved drug or device includes (but is not limited to) that the investigational product is intended for a "serious or immediately life-threatening disease or condition"[8] and there are "no comparable or satisfactory alternatives."[9]

The regulations for expanded access are codified at 21 CFR 312.300-320 for investigational drugs and at 21 CFR 812.36 for investigational devices. Additionally, the Project BioShield Act of 2004[10] permits the FDA to authorize the use of an unapproved product during a declared domestic, military, or public health emergency.[11] In this case, "emergency" within the meaning of the Project BioShield Act is different from the use of "emergency" within the meaning of expanded use regulations for the use of a test article on a human subject in a serious or life-threatening situation.

Expanded Access to INDs

The FDA has issued draft guidance titled "Expanded Access to Investigational Drugs for Treatment Use – Qs & As"[12] and, under current regulations, there are actually three categories of expanded access for INDs:

- Expanded access for individual patients, including for emergency use[13];
- Expanded access for intermediate-size patient populations[14]; and
- Expanded access for large patient populations under a treatment IND or treatment protocol.[15]

In the "Expanded Access" draft guidance, the FDA describes types of regulatory submissions that can be used to obtain expanded access to an investigational drug, saying that, "[f]or each category of access, there are two types of regulatory submissions that can be used: (1) an *access protocol* submitted as a protocol amendment to an existing IND (i.e., an access protocol), or; (2) a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use (i.e., an *access IND*)."[12,16]

Emergency Use of an IND

Under 21 CFR 312.310, the FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician in an emergency situation. In the case of an emergency, the FDA may authorize the emergency use by telephone.[17]

In its "Expanded Access" draft guidance, the FDA interprets this regulation to mean that "it is appropriate to request individual patient access using the emergency procedures described in 21 CFR 312.310(d) when treatment of the patient must occur within a very limited number of hours or days."[12]

Expanded Access to IDEs

There are four regulatory means by which the FDA may allow for the expanded use of an investigational device: continued access, treatment use, compassionate use, and emergency use. Continued access may be allowed after a pivotal trial for an IDE is completed and before the marketing application has been approved by the FDA, provided that there is either (a) a public health need or (b) the preliminary evidence suggests that the device may be effective and there are no significant safety concerns.[18]

Prior to the completion of a pivotal trial an investigational device may be made available to additional patients for treatment use provided that:

- the patients have a life-threatening or serious disease;
- there are no acceptable alternatives;
- there is a controlled clinical trial for the same use; and
- the sponsor is actively pursuing approval.[18]

Compassionate use of an investigational device may be approved by the FDA in situation when (a) there is a serious disease or condition, and (b) there are no acceptable alternatives.[18]

Emergency Access to IDEs

Under 21 CFR 812.35(a), a physician may use an investigational device to protect the life or physical well-being of a subject in an emergency if the physician concludes that:

- the patient has a life-threatening condition that needs immediate treatment;
- no generally acceptable alternative treatment for the condition exists; and
- because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.[19]

In its "Information Sheet Guidance for IRB, Clinical Investigators, and Sponsors—Frequently Asked Questions About Medical Devices," the FDA suggests that, in such an event, the physician should follow as many of the following patient protection procedures as possible:

- Informed consent from the patient or a legal representative;
- Clearance from the institution;
- Concurrence of the IRB chairperson;
- Assessment from an independent physician; and
- Authorization from the IDE sponsor.[19]

The criteria for compassionate or emergency use of an unapproved drug or device includes (but is not limited to) that the investigational product is intended for a "serious or immediately life-threatening disease or condition" and there are "no comparable or satisfactory alternatives."

Conclusion

For a patient with a serious life-threatening disease or condition, expanded access to an investigational product may offer an option when there are no satisfactory non-investigational alternatives. In 1987, the FDA began to authorize limited access to investigational drugs, which has gradually expanded to include devices with statutory authority to act in the case of a national emergency.

In 2014, there are a variety of options for off-protocol access to investigational drugs and devices. Although most expanded uses require prior submission and approval by the FDA, 21 CFR 812.35(a)(2) allows for the off-protocol use of an investigational device when there is no time for FDA or IRB approval, and when the deviation from the investigational plan is necessary to protect the life or physical well-being of a subject in an emergency.

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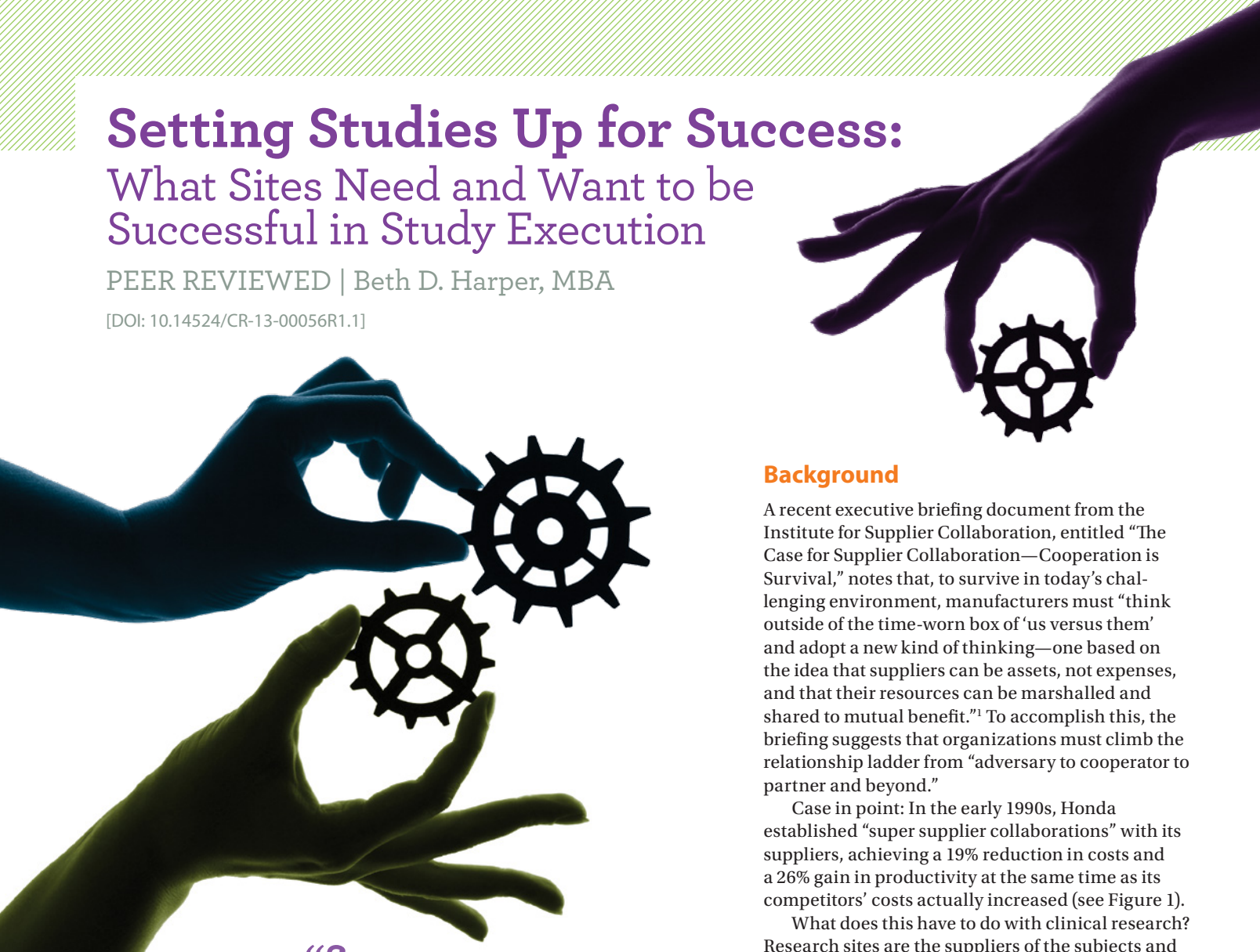
Setting Studies Up for Success:

What Sites Need and Want to be Successful in Study Execution

PEER REVIEWED | Beth D. Harper, MBA

[DOI: 10.14524/CR-13-00056R1.1]



"Site engagement" and "strategic site partnerships" are but a few of the trendy phrases capturing the attention of the clinical research enterprise these days, especially as it continues to grapple with the issue of poor trial performance. Sponsors and contract research organizations (CROs) continue to look for ways to improve and differentiate their relationships with investigative sites as protocols become increasingly more difficult to enroll and implement. In addition, industrywide initiatives aimed at giving investigative sites more of a voice are gaining momentum, and sites are welcoming the opportunity to discuss ideas that directly affect them and their bottom line.

This article explores the evolution of sponsor/CRO-site relationships over the last 15 years—what has and has not changed and where the opportunities for improvement lie from the perspective of a veteran clinical research professional who has dedicated the better part of her career to optimizing enrollment and site performance. Also highlighted are results from a recently completed meta-analysis, which provide valuable insight into what sites need and want from their partners to successfully execute clinical trials.

Background

A recent executive briefing document from the Institute for Supplier Collaboration, entitled "The Case for Supplier Collaboration—Cooperation is Survival," notes that, to survive in today's challenging environment, manufacturers must "think outside of the time-worn box of 'us versus them' and adopt a new kind of thinking—one based on the idea that suppliers can be assets, not expenses, and that their resources can be marshalled and shared to mutual benefit."[1] To accomplish this, the briefing suggests that organizations must climb the relationship ladder from "adversary to cooperator to partner and beyond."

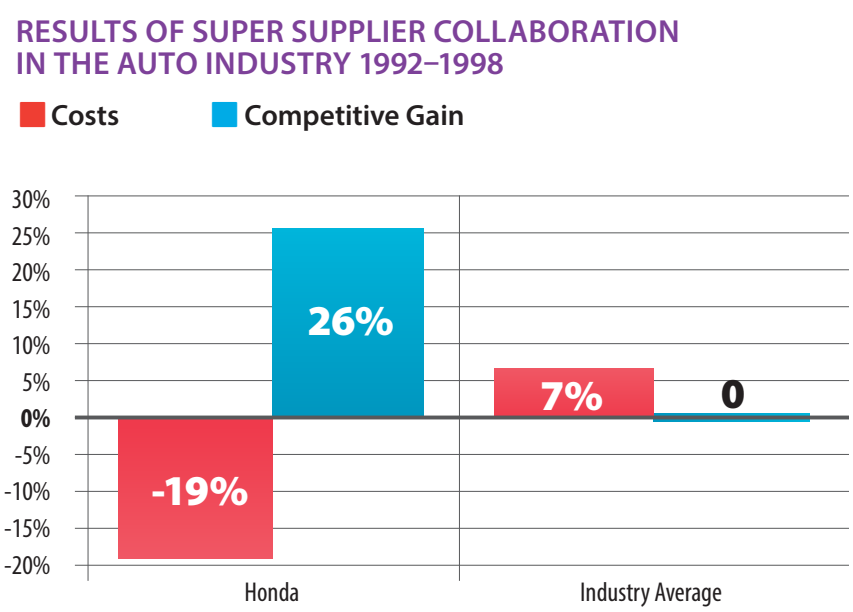
Case in point: In the early 1990s, Honda established "super supplier collaborations" with its suppliers, achieving a 19% reduction in costs and a 26% gain in productivity at the same time as its competitors' costs actually increased (see Figure 1).

What does this have to do with clinical research? Research sites are the suppliers of the subjects and the subsequent data upon which answers to important research questions are generated—no sites, no subjects, no data, no answers. Across the industry however, I have observed that sponsors and CROs often treat research sites as adversaries instead of partners. By re-examining relationships with investigative sites, sponsors and CROs can move from contentious to collaborative relationships, and ultimately improve on the bottom line.

Perspectives from a Long-Time Site Advocate

What do research sites need and value most from sponsors and CROs? What is and is not working in the current approach? What can the industry do to set suppliers up for long-term survival and maximum success? Such are the questions that sponsors, CROs, and sites alike are asking as they strive to remain competitive and viable in today's world—one filled with more complex protocols, a predominance of electronic communications, and looming questions as to the effects risk-based and remote monitoring practices will have on traditional site relationships.

FIGURE 1. Why We Should Care About Keeping Our Suppliers in Business[2]



Further, these are questions I have been exploring for nearly two decades, in a quest to optimize trial performance by enhancing sponsor/CRO-site relationships. In 1997, I published the results of an ACRP member survey evaluating the effectiveness of performance incentives on improving site performance in clinical trials.[3] The paper explored the trial performance frustrations of sites, sponsors, and CROs, and looked at different practices that sponsors and CROs were employing in an effort to get better enrollment, data quality, and protocol compliance performance from the sites.

That survey asked 1,623 ACRP members—including clinical research coordinators, clinical research associates (CRAs), site managers, CRO managers, and sponsor managers—what type of incentives they were providing sites and whether they were effective in improving site performance. The survey also asked sites to share the types of performance incentives they received, and whether they were perceived as valuable. If not, what other types of support would be more successful? [Note: The term "incentive" was used loosely to describe any type of tactic used to improve enrollment and overall site performance, whether it was directed to the sites or to the patients themselves.]

The survey garnered 550 participants for a 34% response rate. The results suggested that there were some disconnects between what sponsor and CRO personnel believed would be effective in terms of improving site performance versus what the sites felt they needed. Table 1 summarizes the key takeaway findings from the survey.

Both CRAs and coordinators agreed that providing medical equipment to site staff to support their ability to execute the trial and encouraging patient-to-patient referrals were incentives that can improve trial performance. However, neither of these relate directly to enhancing study coordinator performance *per se*.

Industrywide initiatives aimed at giving investigative sites more of a voice are gaining momentum, and sites are welcoming the opportunity to discuss ideas that directly affect them and their bottom line.

Whereas CRAs believed providing financial incentives or bonuses to the sites improved performance, the study coordinators in this survey disagreed (with a 14% difference in terms of the perceived value and effect on performance as rated by the CRAs versus the coordinators), and they provided a variety of reasons for doing so. Further, items valued by the coordinators, such as involving them in the protocol design or providing food, treats, or other "thank you" gestures, were deemed by the CRAs as not effective.

The article explored the results and rationale behind some of the perceptions in greater detail, which will not be reiterated here other than to note that sponsors and CROs may often make assumptions about what sites need, want, and value. However, in my experience, if you actually ask the sites (in this case the study coordinators and site managers), they may have vastly different views. I believe that if sponsors and CROs want to be effective in enhancing site performance, they need to offer things of value to the sites.

TABLE 1. Summary Results of the 1997 ACRP Member Survey on Site Performance Incentives

	Performance Incentives Used and Deemed Effective by CRAs	Performance Incentives Not Used by CRA Because They are Deemed Not Effective	Performance Incentives Not Used by CRA Due to Minimal Experience with Providing the Incentive
Performance Incentives Valued by Study Coordinator	• Provide medical equipment • Encourage patient-to-patient referrals	• Provide food, treats, niceties (17%) • Involve in protocol design (11%) • Keep medical equipment (11%) • Provide and keep business equipment (6%) • Involve in case report form (CRF) design (5%)	• Provide continuing education opportunities
Performance Incentives Not Valued by Coordinator	• Provide financial incentives (14%)	• Provide promotional items for patients	• Pay for physician referrals (43%) • Provide a dedicated coordinator budget (7%) • Facilitate coordinator publications (5%)

Sponsors and CROs often treat research sites as adversaries instead of partners. By re-examining relationships with investigative sites, sponsors and CROs can move from contentious to collaborative relationships.

Many of the incentives employed in the past (e.g., providing gift baskets to sites and promotional items to patients) are no longer in practice due to various regulatory restrictions governing investigative site payments and interactions (such as the Pharmaceutical Research and Manufacturers of America Code on Interactions with Healthcare Practitioners and the Sarbanes-Oxley and Sunshine Acts). Meanwhile, strategies such as involving sites upfront in the protocol and CRF design are gaining more traction, while others still have not really evolved to their potential. Nonetheless, this 17-year-old ACRP member survey set me on a career-long endeavor aimed at trying to better understand what sites really need and want in order to be successful in implementing clinical trials. Certainly, I am not alone in this mission.

Sponsor/CRO-Site Relationships in the Spotlight

Numerous articles and industry surveys have helped to shape the discussion about effective sponsor/CRO-site relationships. For example, since about 2003, CenterWatch has surveyed sites every few years to collect ratings of which sponsors and CROs they like working with best (see Table 2).[4] These surveys highlight the characteristics that sites value in such relationships.

A snapshot of results from the 2009 CenterWatch survey[5] shows that sites place high value on:

- Professional, well-trained monitors/CRAs
- Organization and preparedness
- Good protocol designs
- Fair grant payment amounts and prompt payments

More recently, the Society for Clinical Research Sites has been surveying its member sites about the sponsors and CROs they believe demonstrate the best partnership commitment. The recipients of the society's Eagle Award are recognized at the annual Site Solutions Summit meeting each October.[6]

TABLE 2. Snapshot of Results from 2009 CenterWatch Industry Survey

	Percent Rate Very Important	Average Sponsor Rating of Excellent	Gap
Has professional, well-trained monitors/CRAs	91%	47%	44%
Is organized and prepared	90%	43%	47%
Provides good overall protocol design	90%	45%	45%
Provides fair overall grant payment amounts	78%	34%	44%
Provides prompt payment of grants	76%	33%	43%

Source: CenterWatch Survey of Investigative Sites in the U.S.: 2009 (n=950)

Since launching its "Prime Site" partnership program in 2008, Quintiles sparked a race among CROs to create strategic site partnerships with select sites around the world.[7] Now, nearly every major CRO has some type of preferred partnership program, and many sponsors too have strategic site network initiatives in place, as they all vie to become the sponsors and CROs of choice.

Indeed, the topic of "creating a strategic partnership with your sites" has become a staple of industry conferences over the last year or so, as sponsor, CRO, and site personnel all campaign for the value and benefits of these alliances.

Why Not Set All Sites Up for Success?

Having observed these industry trends, the industry is placing heavy emphasis on these strategic partnerships, particularly given that there are a finite number of investigative sites to begin with and that, realistically, they cannot all be "strategic partners" with each sponsor or CRO. That is not to say there isn't inherent value in greater information transparency (i.e., sharing of upcoming trial pipeline so sites can do better capacity planning) and operational efficiencies (e.g., streamlined contracting process) in exchange for more predictable enrollment performance and dedicated site resources.

However, from my perspective, why not set every site up for success with every trial? I question why the relationships have to be "strategic" ones in order for all sites to benefit from better training, communication, professionalism, budgets, and payments.

Faced with these recent trends, and combined with insights from the original ACRP member survey that I conducted, I have continued to wonder if I could quantify in exact terms what sites really need, want, and value when it comes to trial execution support that can have a true effect on the bottom line by delivering timely and high-quality study results.

Trial Troubleshooting Provides Some Insights

Having conducted several hundred site needs assessment surveys as part of trial rescue and rejuvenation support activities when studies were in trouble, I have found that there are five key areas where sites seek better support from sponsors and CROs (more on this below). Site needs assessment surveys are one of a set of diagnostic or trial troubleshooting methodologies employed when a study is lagging behind in enrollment or facing other performance issues (e.g., higher than expected protocol deviations, slow data entry and query response times, etc.).

The site personnel (investigator, coordinator, research nurse, site director, patient recruitment specialist, and other relevant ancillary personnel) are surveyed electronically (or in some cases interviewed live) to get their perspectives on what they believe are the biggest barriers to study execution success. Site staff are also asked to prioritize the value and effects of a variety of potential interventions that help the study teams to design the most appropriate types of training, tools, and support.

Although many of the site needs assessment surveys are structured differently depending on the needs of the study, I reviewed my archives to see if I had any data that could be pooled to answer the questions about what sites really need, want, and value. I identified approximately 25 study-specific needs assessments surveys conducted between 2006 and 2013 in which the questions were asked in a similar enough fashion to enable the results to be pooled. These results reflected the opinions of some 1,500 clinical research professionals in varied roles across 41 countries.

The survey content was structured to ask sites the following types of questions:

- What are your top training needs regarding the study?
- What do you perceive as the top challenges or barriers to enrollment? To seamless study implementation?
- If time, money, or resources were unlimited, what three things would you recommend to the sponsor or CRO to help improve enrollment and your ability to implement the trial?

Although the issues for each particular trial were different, the findings revealed five key areas where the sites consistently voiced a need for greater support. To be successful in implementing clinical trials, sites rated the following as their top priorities:

- Obtaining a better understanding of the target patient population and the specific eligibility criteria
- Receiving help in "translating the protocols into practice" in terms of more practical information on how to interpret the schedule of events and protocol procedures
- Receiving more support (resources, job aids) for identifying and pre-screening patients
- Receiving help for the development and implementation of recruitment action plans
- Learning how to better communicate the study effectively and receiving additional help with the patient/family education process

In my experience, the results of these surveys lead study teams to identify and prioritize the interventions used to help get studies out of "rescue mode," but I believe the industry is missing a huge opportunity not to provide this type of support up-front to all sites when commencing a study.

Developing job aids to support pre-screening and study implementation, ensuring sites are appropriately compensated for all of the pre-screening effort required to recruit patients with more and narrower eligibility criteria, and aiding the patient education and informed consent process all seem reasonable and appropriate measures to apply proactively to enhance enrollment and site performance. Furthermore, I don't think anyone can argue that these site requests would violate any good clinical practice or other regulatory guidelines, nor would they be perceived as incentives that could induce noncompliant behavior on the part of site personnel.

These results, combined with the other industry surveys, can further reinforce that what sites need, want, and value is actually pretty basic in nature, and that these elements for building and conducting quality studies fundamentally haven't changed dramatically over the years.

Conclusion

I do not dispute the value of having more strategic sponsor/CRO-site partnerships, but I believe the trial execution level is where the "rubber really meets the road." Although every trial is unique, the themes arising from the site needs assessment meta-analysis suggest that sites want more and better training, job aids, and financial support to enable them to more confidently communicate and implement trials. This presents real, tangible, immediate, and meaningful activities that sponsors and CROs can undertake to create more super-supplier collaborations.

Whether or not the site is a "strategic" or "preferred" site of the sponsor or CRO, I believe that all sites can vastly improve their productivity if sponsors and CROs focused their investments in these key areas. More productive suppliers, better relationships, and faster enrollment, data, and answers…priceless.

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The Need for a Standards-Based Approach to Staff Workload Tracking: A Case Study

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[DOI: 10.14524/CR-13-00058R2.1]

Staff effort-tracking, otherwise referred to as staff workload assessment, in clinical trials is commonly defined as the process of objectively quantifying the time it takes for staff to complete study tasks in order to determine the costs of conducting clinical trials and support equitable workloads among staff. It employs a data-driven approach, whereby staff record the time they spend on trial activities. It is a topic that has become increasingly popular, as sites look to gain greater control over operations and support more balanced workloads.[1–3]

This article addresses the benefits and challenges that sites face when implementing staff effort-tracking processes. It also examines a case study of organizations that collaborated to establish goals and define processes and tools, demonstrating the need for a standards-based approach to effort-tracking.

Staff Effort-Tracking Overview: BENEFITS

Sites have identified two main motivations for tracking staff effort in clinical trials:

- More accurate trial budgeting and negotiation with sponsors
- Proper workload planning for staff to ensure efficient and effective outcomes of clinical trials

Many site budgets are too low to provide adequate compensation for the work completed. Sites do not have proper insight into the time required for certain trial activities and, therefore, do not have insight into the associated costs of those activities. Furthermore, negotiations with sponsors can be difficult without documentation to justify the time it takes for staff to complete trial activities.[3]

Workload planning is another value of tracking staff effort. Organizations can more easily grasp how many staff members are needed to ensure effective and compliant outcomes for trials. This can help sites more accurately estimate the number of trials they can conduct at a given time.[3]

Without staff effort-tracking, an organization may struggle with determining capacity and scope for an individual employee. This can lead to staff members who are overloaded or underemployed in their roles. Furthermore, workload planning can be an important element in efforts to maintain staff morale.

When the Indiana University Simon Cancer Center conducted a staff survey, one of the largest frustrations among staff was an unbalanced workload. Also, the center has looked to effort-tracking as an opportunity to identify where a staff member may need more training in his or her role.[4]

Tracking staff effort can also have a positive effect on staff hiring. It can provide the data needed to justify more staff if current staff members are overwhelmed in their workload, or are dedicating too much time to tasks that are outside the scope of their roles.[5]

The value of proper workload planning and hiring can be especially valuable in the current climate of increasing trial complexity. Respondents to a recent CenterWatch survey conducted among 269 coordinators reported that the typical trial has become more demanding.[6]

Staff Effort-Tracking Overview: CHALLENGES

Although there is clear value behind tracking staff effort, the process has yet to become widely adopted across sites,[3] largely due to a lack of foundational elements that must be put in place before site staff can be confident in the process of collecting and analyzing data. The following are common challenges that sites face in tracking staff effort:

Without staff effort-tracking, an organization may struggle with determining capacity and scope for an individual employee.

Determining the Types of Data Needed

Knowing where to begin in terms of data collection can be difficult, because many organizations may not know the questions they are trying to answer and, therefore, don't know what data to collect. Are they trying to define where the most time is spent so they can evaluate potential process changes to make roles more efficient, or to justify adding staff members? Or do they want to redefine job descriptions and split the workloads across multiple groups?

Further, how detailed should the tasks be to provide quality data from which an institution can glean valuable information and put solutions into action? Should the data be an overview of high-level tasks performed or provide more detail (e.g., patient education versus patient education about lab results, patient education about treatment options, etc.)?

Although it may appear advantageous to seek detailed data, if tasks are too detailed, it could become difficult for staff members to record data accurately and consistently. Organizations must find a balance when determining the types of data to collect.

Dedicating Staff Time

Although preferred methodology has been identified, such as time-and-motion studies,[3] such methods have been considered by many to be too time consuming, as they require staff to manually document their efforts.[3] If the level of detail required to be recorded is too high, it can also be time consuming for staff members to record it. The potential consequences are that staff could enter data inconsistently (or not at all), and the resulting measurements may not be as accurate as desired.

Gaining Staff Participation

Obtaining staff participation can also be challenging for various reasons. The work of effort-tracking may seem demeaning or be too time consuming.[8]

Another challenge can be the staff perception that they are being micromanaged, or that the data will be used to reprimand them. For example, if most nurses take 30 minutes to complete a task, but one staff member consistently takes 60 or more minutes to complete the same task, would that staff member be seen as being inefficient? This is a real concern among staff.

Such negative perceptions can ultimately hamper staff participation, and participation is key to collecting useful data and taking action.

Maintaining Data Quality and Consistency

Another challenge involves properly categorizing tasks so they are clear and consistent across an organization. This requires understanding the tasks performed across studies, and clearly communicating definitions to staff to ensure that data are recorded properly. Also, the system in which staff members record their time must be easy to understand and use. Without consistent data, an organization is unable to rely on the results to provide accurate analyses.

Overcoming Challenges Through Established Standards: A Case Study

Given the clear benefits, yet significant challenges, in implementing effort-tracking practices, a standards-based approach can assist organizations in quickly adopting processes that result in quality data and actionable analyses. Furthermore, establishing common datasets enables organizations to accurately compare their data to peer organizations and identify inefficiencies in operations.

Recognizing the benefits, organizations have begun to establish standards-based approaches to staff effort-tracking. In the United Kingdom, for example, the European Organization for Research and Treatment of Cancer worked collaboratively with cancer centers to identify a standard set of tasks and subtasks for tracking effort among staff. A tool was developed with the common dataset and piloted across numerous organizations. The work has culminated in standard tools available for use across sites.[2]

Similarly, a group of research organizations in the United States collaborated under the umbrella title of Onsemble[9] to devise an approach that could overcome the challenges associated with staff effort-tracking. The group consisted of seven academic research organizations that employ a common clinical trial management system.

The remainder of this article focuses on the work done by the Onsemble group to create a standard effort-tracking approach. It also illustrates how the approach was implemented, and the resulting effects on operations at one participating institution.

Determining What Needs to Be Collected and Creating a Common Dataset

The Onsemble group first addressed the idea of creating standards by focusing on establishing a common dataset. To do so, the group members asked questions they wanted answers to at their institution, such as "How much time does it take to open a new trial?" and "How much time does it take to open a trial to accrual?"

The dataset gathered details that extended from study startup throughout the lifecycle of the trial to closeout. From there, the organizations set out to identify how much time is spent on specific tasks and who performs them. Furthermore, the group measured other variables related to the study, including sponsor type, phase, and whether or not it was managed by a contract research organization.

FIGURE 1. Nursing Effort in Hours on Active Industry Trials

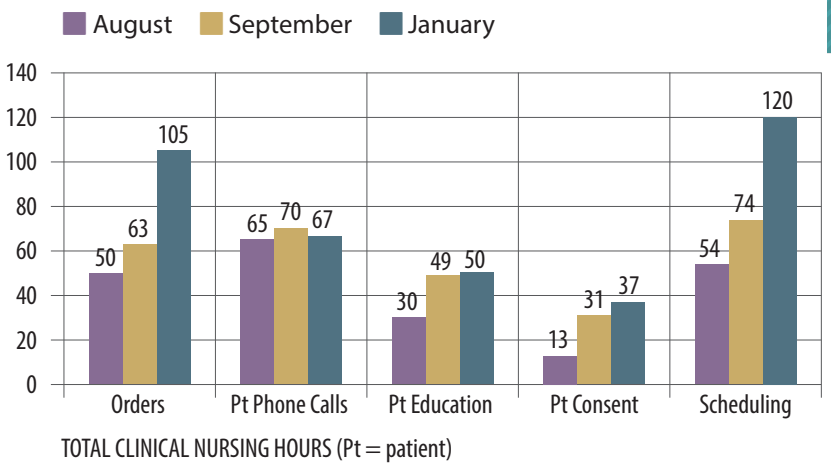
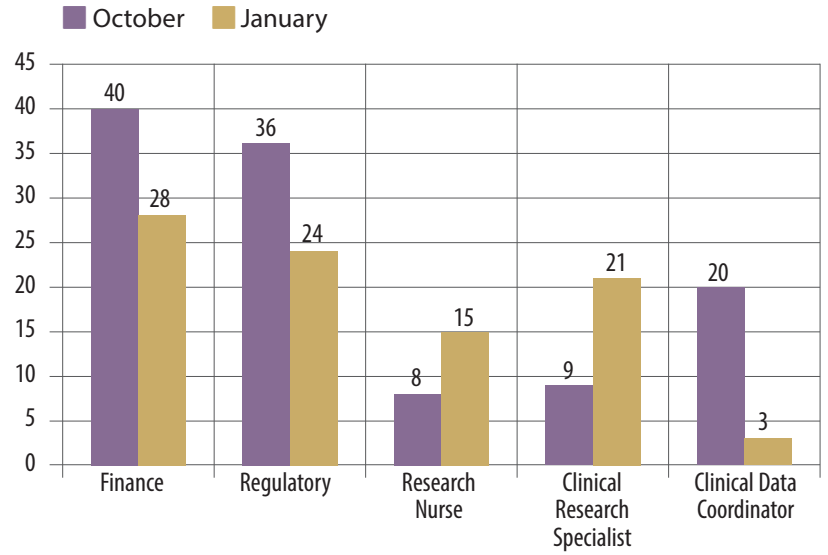


FIGURE 2. Startup: Average Hours per Full-Time Employee per Role



Once the goals of the collaboration were set, the organizations worked to define stages of a trial that were important to track. These included:

- Startup
- Active
- Follow-up
- Closeout

Categories were then defined and put into the following buckets:

- Budgeting
- Contracting
- Data management
- Regulatory
- Clinical activity/coordination

The group then also defined tasks within each category, such as amendments, patient care, vendor inquiries, serious adverse event management, and contract negotiation.

Saving Staff Time and Maintaining Consistency with a Standards-Based Tool

To implement effort-tracking processes that would not impede research staff in their day-to-day activities, a standard effort-tracking tool was developed based on the defined stages, categories, and tasks.

With the tool, staff were able to log into a system that allowed them to enter data according to the stage and category of trial activity, guiding them in their data entry and helping to ensure consistent data among staff.

Indiana University Simon Cancer Center, an Onsemble collaboration participant, also created a corresponding user guide[12] to ensure that staff were knowledgeable about the types of information being recorded and the corresponding definitions.

Obtaining Staff Participation

Indiana University Simon Cancer Center initiated a six-month pilot project to track industry-sponsored studies. The center began by recruiting volunteers from different operational areas.

When requesting volunteers, the center said that the pilot project was an opportunity for staff to demonstrate challenges in their workloads. Staff members saw it as a chance to justify frustrations with their workload and show how much time was spent on certain activities. Volunteers included a research nurse, a finance representative, a regulatory representative, and a study coordinator. Each participant tracked his or her study activity for six months.

Following the pilot, university leadership mandated the use of effort-tracking at the organization. To promote continued engagement, the center has shown the recorded data to staff in the form of reports to demonstrate that their efforts are being taken into account.

In addition, the Holden Comprehensive Cancer Center, part of the University of Iowa Hospitals and Clinics, recently implemented the standard effort-tracking tool that was developed with guidance from the Onsemble collaborative group. The center took a similar approach to that of Indiana, and recruited volunteers by communicating it as an opportunity to help coordinators get a handle on their workloads. The center received six volunteers from regulatory and clinical research associate areas.

The feedback gathered from staff using the tool to track their efforts has included a feeling of accomplishment, surprise at how much time was

The feedback gathered from staff using the tool to track their efforts has included a feeling of accomplishment, surprise at how much time was spent on certain activities, and recognition of the minimal amount of time it took to record activities.

spent on certain activities, and recognition of the minimal amount of time it took to record activities. The Holden Comprehensive Cancer Center plans to include required effort-tracking as part of its team's daily performance goals in 2014.[10]

Assessing the Overall Effect on Operations

The Indiana University Simon Cancer Center recorded a multitude of data that gave unique insight into roles and activities over its six-month pilot project.[5] This article discusses a couple of examples of actionable data that the center recorded.

As one example, the results of the data showed that research nurses were spending too much time on administrative tasks (see Figure 1). Recognizing the need for these nurses to refocus their efforts on patient care, the center used the statistics to justify hiring an additional full-time employee.

In a second example, the data showed that significant time was spent on financial tasks to open a study, greater than that of regulatory efforts (see Figure 2). Knowing these statistics, the center has been able to justify higher budgeting for these tasks, and is able to provide documentation for startup costs with sponsors, supporting more streamlined negotiation processes.

Future Direction of Staff Effort-Tracking

The standards-based approach employed by the collaboration presents an opportunity for organizations to learn more by comparing their measurements with other organizations, and to identify opportunities for greater efficiencies in workloads. As a direct result of this work, a platform has been created that offers all academic organizations a free standardized tool for tracking and analyzing staff effort. The tool also offers users at the organizations the ability to compare their anonymized data.[11]

Conclusion

Given the benefits, yet significant challenges, of staff effort-tracking, sites clearly need defined processes and tools to effectively adopt the practice. As demonstrated by the work of the Onsemble collaboration and the results at Indiana University Simon Cancer Center, a standards-based approach assists sites with establishing clear goals, recording actionable data, and realizing significant benefit.

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The CRC and Form FDA 1572

The times, they are a-changin'

As we've noted in past columns, being a research coordinator means working with a lot of different people and wearing a lot of different "hats." One hat that coordinators often find to be tedious to wear is that of the regulatory specialist. The amount of paperwork required to begin a new trial is staggering, and the Food and Drug Administration (FDA) Form 1572 (the "Statement of Investigator") is second in difficulty and confusion only to the institutional review board (IRB) application.

Since the Form 1572 was first introduced as part of 21 CFR 312.53 in the *Code of Federal Regulations,* a lot of questions have concerned how to adequately complete it. One bit of good news—for people new to research who may not yet be as familiar with regulations as they should be—is that the Form 1572 is required only for clinical investigations conducted under 21 CFR Part 312 (regarding the Investigational New Drug application and regulations). This means that you need to fill it out only for drug studies. If you were the naïve coordinator who prepared and submitted it to a sponsor as part of your device study documentation, you should find a training class as soon as possible.

From the 1572 Guidance document on the FDA website,[1] you can find helpful notes on filling out the specifics of the form. Although that should be enough instruction to properly complete the document, the FDA has also published a Frequently Asked Questions document[2] to provide answers to any still-lingering doubts.

The Invisible Hand

One of our favorite articles in coordinator literature is "The Invisible Hand in Clinical Research: The Study Coordinator's Critical Role in Human Subjects Protection," published in 2002 in *The Journal of Law, Medicine & Ethics*.[3] For full disclosure, Claudia participated in this research, not as part of the study team but as one of the participants. When Claudia participated in the focus groups that contributed to the findings, she was enthusiastic that someone was taking the time to ask coordinators about their role in research and listening to what they had to say. Sometimes the role of research coordinator can feel very lonely, and this was one of the first times she had the opportunity to discuss the challenges of her work with a group of people who understood what she was experiencing.

From her perspective, one of the key points of the article is the central role of the study coordinator. Research coordinators interact with most everyone involved in the study, including the subjects, IRB members, monitors, other research team members, and internal and external customers. The article has proven to be a useful one in presentations discussing the importance of all members of the study team.

According to the article, "Focus group participants consistently described their position in terms of complex and potentially conflicting obligations to various parties." No matter who you are on the research team, you feel the compounded stress from the requirement to balance patients' safety and rights, the needs of the investigator, the urging of the sponsor or contract research organization, and the never-ending stacks of paperwork.

Coordinators have to do it all, and get it all right, or the study is doomed. One way to ensure that coordinators get it right more often than not is through training. The "Invisible Hand" article advocates for the research coordinator to be involved in human research ethics training, and it was one of the first to focus on the role of the coordinator regarding human subjects protection.

Being a research coordinator means working with a lot of different people and wearing a lot of different "hats." One hat that coordinators often find to be tedious to wear is that of the regulatory specialist.

Moving On From the Good Old Days

In the early days of clinical research, when requiring human subjects protection training was just beginning, there were questions as to whether the coordinator needed to be included in this training. At that time, the usual recommendation for filling out the 1572 was to include the pharmacist on the form, but not the coordinator. The more recent guidance recommends that people who will contribute significantly to the study be added as sub-investigators.

Today's norm adds the coordinator, but not the pharmacist.

> For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical studies that are ongoing concurrently at an institution. Because the pharmacist would not be making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a sub-investigator in Section 6 of the 1572, but he/she should be listed in the investigator's study records.
>
> Generally, a research coordinator has a greater role than any pharmacist in performing critical study functions and making direct and significant contributions to the data. For example, the research coordinator often recruits subjects, collects and evaluates study data, and maintains study records. Therefore, the research coordinator should usually be listed in Section 6.[2]

One disclaimer, some sponsors do not require the CRC to be on the 1572 and it may be their policy not to include the CRC. This document quote is a guideline, after all.

Times have certainly changed from just a few years ago. Today's coordinators are efficient, intelligent professionals who contribute significantly to the study. That is certainly an advance from 12 years ago, when the "Invisible Hand" article was published. Although the coordinators of that time were equally qualified, they were not always recognized as being so.

Conclusion

As the article succinctly notes, the term "coordinator" is "often noted to be the best descriptor of the job." We are coordinators because we coordinate the needs of the trial with the needs of the subjects. We coordinate the delivery of the lab samples, the FedEx pickups, the training sessions, the meetings, and the needs of everyone around us.

Although you should always note that the FDA's guidances are left to interpretation and follow the opinion of your sponsor, principal investigator, or local practice, in most circumstances you should go ahead and list yourself in Section 6 of the FDA Form 1572. After all, you are a valuable member of the team and you make a significant contribution to the research performed both at your site and around the world. It's written in the guidelines.

By signing the 1572, the investigator is making a legal declaration that these are facts. Although there is an obligation to being formally noted, it also signifies that you take your duties as research coordinator very seriously and deserve to be recognized as a professional.

No matter who you are on the research team, you feel the compounded stress from the requirement to balance patients' safety and rights, the needs of the investigator, the urging of the sponsor or contract research organization, and the never-ending stacks of paperwork.

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Disclosure

The NC TraCS Institute at the University of North Carolina is the academic home of the National Institute of Health's (NIH's) Clinical and Translational Science Awards (CTSA) program, grant number 1UL1TR001111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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CRACKING THE CODE
for Clinical Trial Recruitment: *A Sponsor's Perspective*

PEER REVIEWED | Deborah Howe | Mary Murray, MBA

[DOI: 10.14524/CR-13-00064R1.1]

Experienced professionals know that when it comes to clinical trial patient recruitment, there is no magic formula. Still, sponsors and leaders of investigative sites alike try in earnest to make strides, move the dial, and even crack the code. In the spirit of successfully enrolling clinical trials, many sponsors continue to seek opportunities to support sites in new and meaningful ways, and to invest in focused efforts that build and improve the quality of the working relationships.

In the March 2013 edition of the *CenterWatch Monthly,* the lead article indicates that sponsors received "good" or "excellent" marks in their overall working relationships with sites, though the article goes on to illustrate that more work is needed.[1] In that same edition, an article about customer satisfaction surveys speaks to the benefits of giving sites a voice, stating that "giving them that platform not only satisfies them, but also allows you to act like a true partner."[2]

In the midst of this industrywide evolution, one sponsor, Bristol-Myers Squibb, did just that. The following case study describes the company's effort to reach out to investigative sites via an electronic global survey, with subsequent use of the feedback to adjust the clinical trial recruitment strategy and tactics.

Identifying Value in Recruitment and Retention Support

The goal of the site outreach was to gain an understanding of site leaders' perspectives on study-related services that sponsors provide, including evaluating which tactics have the greatest and least effect on site performance in studies. A number of questions within this survey contained a list of pre-identified tactics that are typically offered to sites to aid in patient identification and support enrollment and retention efforts.

Based on the sites' survey feedback, tactics were evaluated by usefulness to the sites. For those tactics ranked as less useful, the sponsor explored the consequences of eliminating them completely, while ensuring minimal negative effect on the site's performance with respect to patient recruitment as well as on the overall working relationship with the site.

For clarity, the survey was not intended to evaluate tactics or efforts generated by the investigative site. For example, in terms of subject retention, many sites focus efforts on "soft skills," such as engaging participants in a high degree of interaction with the principal investigator. This survey was not intended to explore the value of these site-based efforts. Rather, the goal was to gain the site leaders' insights and opinions regarding the sponsor-provided items and tactics for clinical trial recruitment and retention.

Methodology

The research was conducted in the form of an electronic global survey containing approximately 50 questions. Disseminated in December 2012, the survey contained questions in the following categories:

- study implementation support
- patient education
- patient comfort items (including travel reimbursement)
- recruitment and retention

TABLE 1. List of Tactics in Each of the Survey Categories

Study Implementation Support	Recruitment and Retention
Newsletters	Template letters and cards to send to referring physicians
Site comparative benchmarks	Referral letters sent on behalf of sites (service to package and mail letters)
Recognition certificates, thank you cards	Presentation materials and support for events aimed at raising awareness among physician referrals ("lunch and learns")
Prohibited/restricted medications	Speaker for special events
Mini-protocols	Sponsor developed and implemented (central) media campaign (includes multiple tactics, such as TV/radio ads, call center)
Drug preparation reference, time and events flowchart, adverse event management guidelines	Template ads and scripts for sites to implement local media campaign (TV, newspaper, print, radio)
Date wheels, reference cards	Funds for site to implement own local media campaign (TV, newspaper, print, radio)
Inclusion/exclusion cards	Media buyer to assist site with purchasing of local market advertising (TV, newspaper, print, radio)
Chart flags	Design and production of print materials to build patient awareness (posters, flyers)
	Sponsor developed and implemented online advertising (search engine optimization)
	Direct mail campaign designed and implemented by sponsor (letters to potential patients)
	Support and advocacy group outreach to raise awareness (sponsor-implemented programs)
Patient Education	**Patient Comfort Items**
Printed patient/caregiver education materials	Clinical compliance support (medication bag, cookbook/recipe book, pedometer, digital timer)
Disease or treatment reference book; video modules for disease or study education	Comfort items to ease the burden of study participation on patients (neck pillow, socks/slippers, bag/backpack, blankets, water bottle)
Live patient information session	Patient/caregiver reimbursement (meals and travel, sponsor provided and managed reimbursement for study patient expenses)
Tools to aid with study compliance (calendar for study visits)	Patient appreciation (birthday card, thank you card)
Visit reminder calls or text messages (centrally managed and implemented)	

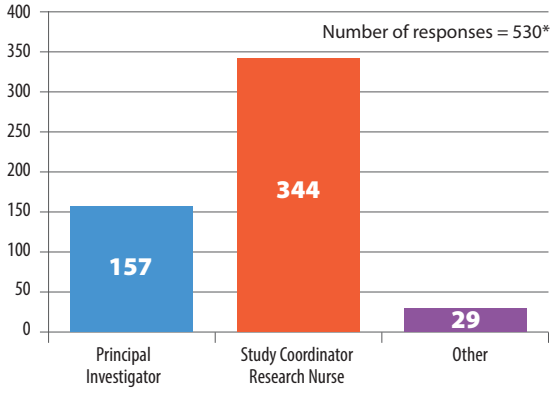
Table 1 presents a list of tactics within each category for which sites were asked to rank the usefulness and assign value. Study-specific branding was one additional category, and included components such as the use of a color scheme, a naming convention, and tagline and/or a logo.

For each applicable category, sites were queried about the acceptability of providing materials in a solely electronic environment. To effectively evaluate and tease out the importance and ranking in each category, questions were presented in a variety of ways. For example, the background and general topics section asked a total of 15 questions aimed at ranking tactics in terms of importance. In each of the five categories mentioned above, respondents then answered seven questions about each tactic, including ranking, investment allocation, preference of electronic versus print formats, assessment of usefulness based on both study and patient characteristics, and the effect of eliminating the tactic altogether.

Several free text questions were included to solicit additional insights related to the earlier questions, including which patient and/or study characteristics influence the usefulness of a particular tactic, how the sponsor's offerings compare to those of other sponsors, and the respondent's rationale for a given response. The free text fields also captured additional commentary following a yes or no response.

Responses were solicited from 4,499 sites across many countries in four key regions: Asia-Pacific, Europe, North America, and Latin America. The survey was open for only a one-week collection period, which yielded 556 (12%) site responses. In the area of market research, this response rate was considered a success.

FIGURE 1. Survey Respondents by Role



**Not all of the 556 respondents answered each survey question; hence, this question was answered by only 530 respondents.*

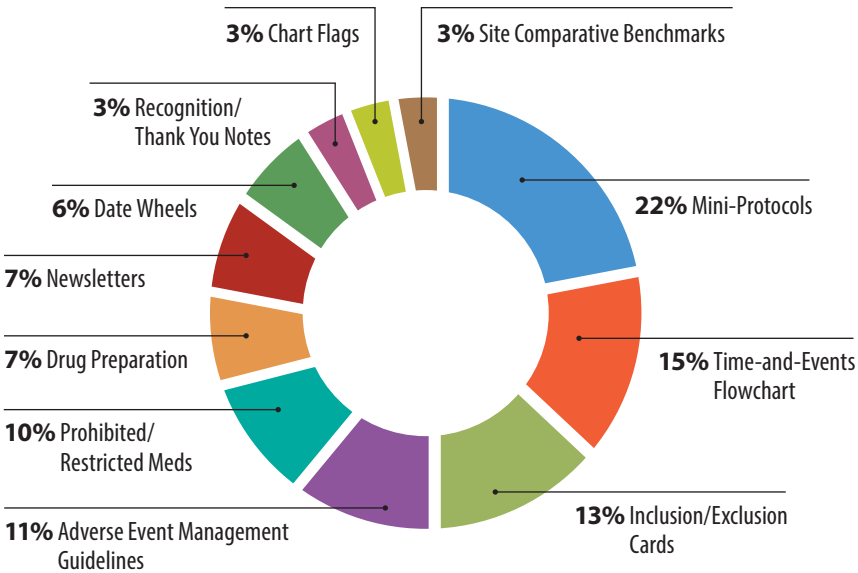
In terms of the role of survey participants, study coordinators or research nurses represented the majority of survey participants at 65%, while principal investigators represented 30% of respondents (see Figure 1). Site responses were evenly distributed across the type of site, such as dedicated research, academic medical center, private practice, and governmental institution. In addition, site responses were fairly evenly dispersed among the geographical regions. More specifically, North America and Latin America were represented by 52% responses, while Europe was at 31%, and Asia-Pacific (including responses from Australia) was at 13%. This was found to match the expectations, as it mirrored the geographies in the studies selected.

To have representation of sites across the six therapeutic areas in the survey sponsor's pipeline, studies were first identified and flagged for surveying as mapped to the therapeutic areas. This list was then further refined to ensure that enrollment had recently ended, or at least had been open long enough to give sites sufficient exposure to the provided materials and tactics.

As for the distribution of respondents, participation was obtained across all of the therapeutic areas, including anti-infective, oncology, autoimmune, cardiovascular, metabolic, and neuroscience. Although oncology site participants were slightly underrepresented, this finding did not skew the overall results; this was an opinion survey and not statistically powered.

In the spirit of successfully enrolling clinical trials, many sponsors continue to seek opportunities to support sites in new and meaningful ways, and to invest in focused efforts that build and improve the quality of the working relationships.

FIGURE 2. Implementation Support Tactics in Ranked Order



Survey Findings

The survey confirmed the sponsor's belief that one of the most important goals for sites is to enhance the patient and caregiver experience, with the acknowledgment that sponsors, as a whole, play a role in helping sites to achieve this objective.

Sites ranked study implementation support tactics (the mini-protocol, standalone time-and-events flowchart) as the top category in terms of value to the patient. The majority of respondents said elimination of this type of support would adversely affect their performance.

As noted earlier, within each category sites were asked to select the most important topics and to assign weightings in terms of allocation of their own investment (in percentages). Figure 2 shows an example of the study implementation support tactics in ranked order. Although these tactics may not be categorized by all as directly related to enrollment or retention, Bristol-Myers Squibb believes that providing tools that help sites efficiently locate study specifics aids in identifying patients. Similarly, company leaders believe that furnishing handy study reference materials, such as date wheels, aids in compliance with study visits, with the ultimate goal of retaining patients.

Regarding some of the other categories, although all respondents ranked highly the importance of sponsor-provided patient recruitment, education, and comfort services, rankings varied in terms of therapeutic area, geographic region, role, and protocol design. For example, sites participating in neuroscience, cardiovascular, and to some extent metabolic studies, placed higher value on recruitment and retention tactics than those in other therapeutic areas such as oncology and anti-infectives. As an example of a role-based nuance, study coordinators expressed concern about eliminating patient education tactics, which they ranked as very important. None of these varying factors seemed to skew the findings.

Based on common themes among the responses in the free text fields of the survey, the sponsor concluded that sites consider some of the items, such as those categorized as "patient comfort" (water bottles, blankets), as "nice to have" rather than important for recruitment and retention.

A surprising finding emerged concerning the utility of study-specific branding. Although sites appreciate that such branding can help differentiate studies at the site level, the greater majority (nearly 75%) of sites indicate that branding has little effect on the ability to successfully complete a clinical study. In other words, only 16% of survey respondents said that elimination of study branding would matter.

Lastly, when sites were asked about receiving items or tactics in an electronic format only, the majority of respondents reported that they prefer to receive hard copies of the study implementation support items, such as the mini-protocols. Sites did comment that providing electronic versions (in addition to the hard copies) of the recruitment materials is helpful in specific circumstances, such as facilitating site-specific changes or for ease of submission to institutional review boards or ethics committees.

Applying Site Feedback to Enhance Recruitment Practices

After careful analysis of the feedback, Bristol-Myers Squibb identified several areas for attention. First, the recruitment team made recommendations to capitalize on the "need to have" items or tactics and to minimize the "nice to have" ones. For instance, based on the information in Figure 2 related to the study implementation support items, a standard core kit was established for future studies that contains the top three ranked items: mini-protocol, time and events flowchart, and inclusion/exclusion reference cards. Mid-range ranked items will be provided to sites based only on specific study need, and items at the bottom of the ranked list will be provided only under special circumstances.

As for patient comfort items, transportation reimbursement was overwhelmingly rated as most valuable, and birthday cards were rated as least beneficial. These findings, along with closer examination of the free text fields, led to the conclusion that the other comfort items (aside from transportation reimbursement) were very much appreciated, but were acknowledged to be more "nice to have" items. For this reason, the traditional comfort items will be eliminated. Based on the survey data and ongoing dialogue with sites, since the risk for elimination may be greater in severe disease states or in specialty populations such as pediatrics, these may become areas for exception moving forward.

In the category of study branding, sites indicated that eliminating branding would not impede successful enrollment. Currently, a small task force is exploring the site feedback more deeply, including examination of the free text comments. This team will seek additional internal stakeholder input as a next step, with the expectation and goal of these efforts being to balance the appropriate application of study branding and the value of differentiating clinical studies. Based on the input gathered, recommendations for streamlining may result in a more holistic approach to branding efforts across all studies.

Applying the logic of providing tactics of greatest impact to the other categories in the survey and rolling out the additional recommendations, Bristol-Myers Squibb expects to yield an annual savings of nearly US $1 million (based on 2012 data).

Conclusion

The value of gaining site insights cannot be underestimated. Using an electronic global survey to gather site feedback proved to be an informative step in understanding this value. More importantly, through the use of the key findings, the sponsor recognized new opportunities and implemented a streamlined set of high-impact recruitment and retention tactics.

Although these findings may not have completely cracked the code, the dial is moving in a direction that points to a better understanding of investigative sites' needs, strengthening the sponsor-site working relationship, and increasing clinical trial enrollment successes.

This site feedback complements the sponsor's additional efforts (ongoing since 2011) to bring the voice of the patient into its clinical trials, in order to meet the whole research team's overarching goal of enhancing the patient and caregiver experience during their participation in clinical studies and beyond.

Among these efforts are organizational changes: First, a dedicated team was created in the global development organization to engage patient advocacy organizations in clinical trial development activities. Second, Bristol-Myers Squibb formed a group to focus on developing a digital strategy and content for connecting patients, caregivers, and providers to various resources, from practical clinical trial matching and navigation to videos that share experiences about the clinical trial process.

By making these organizational changes and by streamlining the recruitment and retention material tactics, the company expects to deliver to site staff and to patients a meaningful clinical trial experience, one that highlights their perspective and offers the items and services they find most impactful. These site-level insights open up opportunities for Bristol-Myers Squibb to envision, consider, and adopt new approaches that it may not even have imagined yet.

Acknowledgments

We would like to acknowledge our colleague, Britt Tella from Bristol-Myers Squibb, and Tracy Blumenfeld from RapidTrials for their significant contributions to the global site survey workstream.

The goal of the site outreach was to gain an understanding of site leaders' perspectives on study-related services that sponsors provide, including evaluating which tactics have the greatest and least effect on site performance in studies.

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A Theory on ***Site Engagement:*** Why Early, Dynamic Interaction with Clinical Trial Investigators Avoids Problems and Saves Money

PEER REVIEWED | Eileen M. Daniel | James M. Denmark

[DOI: 10.14524/CR-13-00057R1.1]

Study site staff want unencumbered access to the sponsor team, and talented trial leaders are naturally inclined to connect with the people involved in their studies, establishing relationships quickly within and across the entire community, no matter how large it may be. These leaders do more than listen and respond; they recognize that effective site support is inexorably linked to the depth of what can be learned about how people actually carry out their responsibilities. Then they face those realities head on.

SPONSOR STORY

Years ago, I resolved to bridge the gap between our study teams and site personnel—a gap that inevitably appears when we partner with contract research organizations to help run our studies. My signature initiative to address this problem was to find ways to engage personally with the nurse who consents our patients or the coordinator who records our data.

Last spring, while preparing a conference workshop on this topic, I was stunned to realize it had been more than a year since I had spoken with anyone at a study site! I shared this sorry fact with the workshop participants, and wondered out loud if I could demonstrate sufficient relevance not to waste their precious time. A hand from the audience shot up. "Call us," the attendee said. "It doesn't matter. We want to hear from you."

I can tell you, that feedback was some motivation for me. I did my homework and made my first call to one of our investigators later that day. I learned something new, agreed to find an answer to a question about a prior study, and called the investigator back the next day with new information. This pattern repeated and, within a few days, I had spoken with seven of our sites, deriving a rich body of feedback that changed my perspective and influenced decisions.

My team members who model this behavior insist it calms what might otherwise be tense problem-solving scenarios and increases responsiveness to enrollment campaigns. However, I am bothered by this persistent question: How can return on investment of sponsor-site contact be measured? It certainly cannot be done justice with a mathematical equation.

One thing I can say with certainty is that my direct and unfiltered interaction with the people who work on our studies is imperative to my ability to do my job.

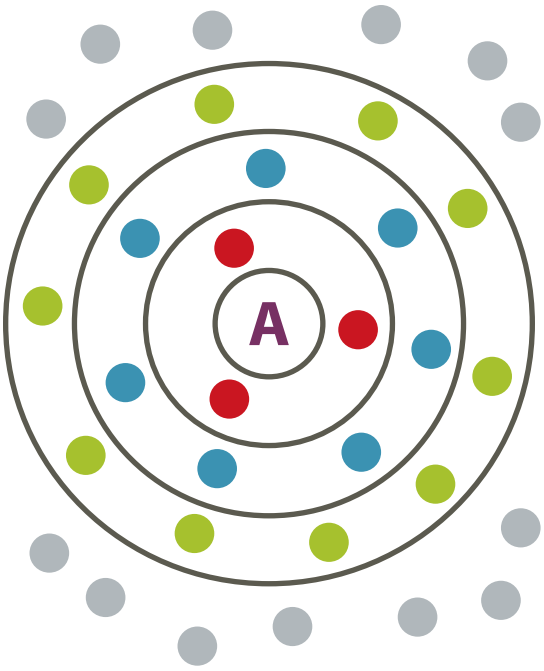
— Eileen M. Daniel, Senior Director, Development Operations, Endo Pharmaceuticals

The clinical research conference circuit has been abuzz with two topics in the past year: risk-based monitoring and site engagement. Although the former is objective and rooted in comfortable parameters, like visit counts and source verification percentages, the latter is an emotion-based, philosophical discussion. Sure, we can quantify the outcomes of site engagement in terms of improved enrollment rates, query resolution times, and the like, but these metric-based performance assessments skip over what it means to cultivate relationships between disparate members of the clinical research enterprise.

Generally, people involved with clinical research are scientifically curious, process-oriented, and driven by the pursuit of data; however, subconsciously they seek to understand their colleagues' motivations and ambitions. This natural behavior results in so many of the person-to-person interactions throughout the workday that are fundamental to human experience, there is little recognition of a need to discuss it.

The problem is these interactions do not extend so naturally across all the people, boundaries, and distances in the larger clinical study context. When the community does not promote, or worse, obstructs natural person-to-person interaction, bad things happen.

FIGURE 1. Coworking



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Engagement Theory

People engage with one another around an ambition or motivation. A person can be directed to talk to a counterpart, but he or she cannot be forced to engage in meaningful discussion. That comes only from mutual interest in a topic or each other.

Identifying a common motive for a study coordinator, regional monitor, principal investigator, and pharmacist in a clinical trial can be a daunting task. Consider a simple example: Ask yourself why you are reading this article. The authors hope you find it interesting and worthy of your time to read it through to the end. To be transparent, we also admit the value of exposure this publication offers and know it will have some effect on our reputations in the industry.

On the other hand, what might be the motives of ACRP for publishing this article? Without a doubt, the association wants its readership to acquire some new insights, but it also needs *Clinical Researcher* to be valued enough that memberships (and therefore, access to the publication) are renewed.

Buried in this example is a common goal of learning that could be easily diverted by the ancillary goals of any of us—reader, author, or publisher. In thinking about strategies to engage people in a study community, those ideas must be evaluated through the lens of each stakeholder.

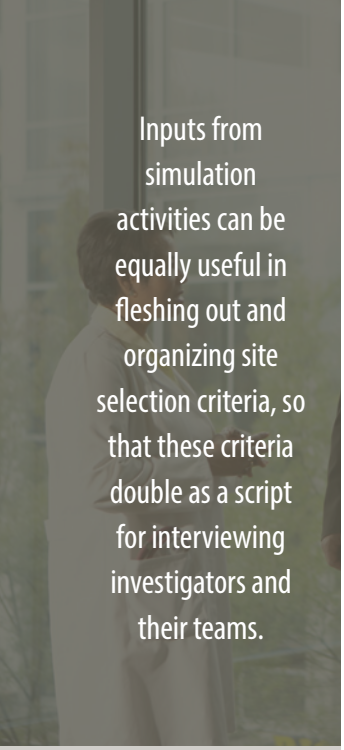
Once a truly common motive is identified, a platform emerges for engaging members of the community. Creating small experiences in which people may share their participation is the first order of business.

Figure 1 is a model on building communities as part of the "coworking" movement, portraying a vibrant community comprising members with differing degrees of engagement. Their level of involvement spikes and drops off over time, with every person traveling along his or her own continuum.

As people mobilize around a motive or ambition (A in the figure), they all start as Observers. An Observer receives information, but is not expected to do anything further. Over time, given additional opportunities to participate, some members of the community will step out of the crowd to join in the discussion. We call these people Attendees: They respond when a question is raised and are present when an event is scheduled. Creating opportunities for one or more Observers to become Attendees is the first objective of building a community.

After some time has passed, with the right occasions available, a number of Attendees may contribute without prompting. These contributions might be suggesting improvements, raising new questions, responding to others, even critiquing. The people in this new subgroup are called Participants. They are the first sign a vibrant community is developing and on the way to self-sustaining.

Identifying a common motive for a study coordinator, regional monitor, principal investigator, and pharmacist in a clinical trial can be a daunting task.



Inputs from simulation activities can be equally useful in fleshing out and organizing site selection criteria, so that these criteria double as a script for interviewing investigators and their teams.

Eventually, one or two of the membership might become "super"-participants. These are highly engaged individuals who identify so strongly with a motive that they engage at all levels with the community at large and gain the respect and trust of everyone. We call these people Champions.

Danger, Danger

This is not a race to the center; nobody is obliged to move through all levels of participation or become a Champion. Some members will become more involved; others will not. Deeper levels of involvement by some may be sustained, or may drop with shifting priorities. This is all okay.

A community manager must recognize when and where participation levels need a boost and create an occasion or inject something newsworthy to keep the momentum going. Further, he or she should intervene when a person or subgroup becomes over-involved, as other members may feel alienation, burnout, or possibly distrust as a result.

Applying this model of engagement theory to the clinical trial arena requires early creative thinking on the part of the sponsor team, as it expands beyond its core members—ideally after the study concept is stable and before the protocol is final. The case examples presented next are timed prior to study start, well before investigator sites receive regulatory paperwork that signals commencement of site activation. They represent some of the most consistently missed opportunities to begin building a community of interest around the clinical program and reaping the benefits of engaged membership.

Case 1: Protocol and Site Feasibility

The site feasibility process is one of the first levers pulled when the clinical trial machine kicks into gear. It spits out hundreds of questionnaires aimed at determining how many patients a site may have, where its centrifuge is, whether it has a pharmacy, how many other studies it may be running in competition, and so on. Responses are sorted; triage meetings take place; and teams are deployed to follow up by e-mail, phone, and fax.

Sites that make the cut receive the paperwork and the pre-study site visits (more on that later). Frequently, feasibility stops there, leaving the illusion that the institution (the site) is known to the sponsor and that a mountain of paperwork already exists to prove it. However, it is all too likely that we have learned little about the people at the site and we have missed an opportunity to influence how they will behave once the study gets started.

Described next are tactics that Endo Pharmaceuticals followed to create an early participation experience that served to establish and deepen relationships. The feedback obtained was used to inform and improve the operational execution of the protocol. Any sponsor or contract research organization can do the same thing.

Involve and Engage Candidate Sites Pre-Study

Referring back to engagement theory, the large pool of candidate sites receiving a feasibility questionnaire would be the Observers. In this example, a subset of investigators was selected to participate in a private online discussion based on their expertise in the therapeutic area and for their passion for patients. Prior to the internal deadline for final protocol, a draft was posted in an invitation-only, secured community that included a discussion forum where specific questions were posed. The trial leader sent a personal e-mail to each investigator with an invitation to join the protocol review team and instructions for accessing the protocol online. A follow-up phone call was made to underscore the importance being attributed to their feedback.

Let Sites Talk to the Study Team and Each Other at Will

Busy investigators reviewed a PDF of the draft protocol from their home or office computer, tablet, or phone. They were asked to answer six questions in the discussion forum, either via the website or simply by responding to e-mails (relayed through the forum to keep everyone updated) on topics of endpoint analysis, lab values, and relevant concomitant medications. The first investigator to respond had the most to say, arguably making it easier for others to weigh in with agreement or counterpoints. Study team members interjected with answers to investigators' questions; then, instead of waiting for the next protocol draft to see others' comments, they could respond right away.

Outcomes

There was one significant, and measurable, outcome: Investigator participation in the protocol review team resulted in the elimination of a secondary endpoint that would not have been feasible to collect; hence, a protocol amendment was avoided. An equally significant outcome, albeit a less quantifiable one, was that a broad segment of the sponsor team was exposed directly to investigator feedback. The forum discussion provided valuable context, and was used as-is to inform final protocol revisions. A commitment was made to evaluate each suggestion and to provide investigators with the rationale for changes that were made.

As sites were activated, new Observers and Attendees (coordinators and investigators) became Participants as they used the forum to pose questions. Study team members replied online and called to ensure all their questions were answered satisfactorily. There was no need to create a process to manage frequently asked questions in a spreadsheet.

Case 2: Pre-Study Site Visit

How would monitors and site staff describe what is expected of them during a pre-study site visit (PSSV), and what is the deliverable? An appropriate answer would be that the deliverable is a monitoring visit report, complete with ticks in all the right boxes and ready for regulatory inspectors.

SPONSOR STORY

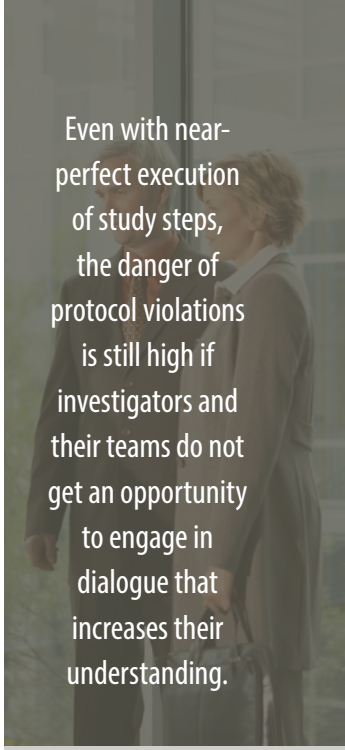
Simulation is another tactic that can enrich the feasibility stage by turning it into an opportunity for early engagement; we do "deep dives" on protocol eligibility criteria by simulating how a site might identify those potentially eligible and acting out the patient experience before the protocol is final. We use the inputs from these exercises to create interactive investigator meeting "how-to" sessions.

Dave Munneke of American Medical Systems says research coordinators are great partners in walking through the protocol from both site and patient perspectives, and they are instrumental in developing case studies for the investigator meeting, now called the study initiation meeting: "We identify learning objectives at the outset and anonymize patient files for coordinators to simulate data collection. We then facilitate dialogue in parallel groups of five to seven participants. The goal is for [meeting] participants to encounter learning opportunities and walk away from the meeting well equipped to conduct the study. This format also allows us to tap into the collective experience of all participants."

Inputs from simulation activities can be equally useful in fleshing out and organizing site selection criteria, so that these criteria double as a script for interviewing investigators and their teams. Such interviews, when done by study team leaders skilled in transforming the question-and-answer routine into actual conversations, are a valuable first opportunity for people to forge relationships based on things they mutually care about. When that magic happens early, bonds are created that survive and thrive through the inevitable peaks and troughs of a clinical study.

People are more comfortable talking about uncomfortable topics when there is a respected and valuable relationship in place. Operational difficulties in clinical trials are largely overcome due to people's willingness to discuss things that aren't working well.

—Kathy Goin, Vice President Clinical Operations, Trevena Inc.



However, what if the deliverable included engagement? To put a sharper edge on a seemingly soft objective, make the PSSV a forum to uncover exactly what principal investigator oversight will mean for the site.

"Sample procedures and forms don't show that," according to Leigh Kerr who directs and oversees clinical studies at Endo. "You can't see actual documents that demonstrate oversight during feasibility or during the PSSV. More and more, we have to go to sites we have not used before, and sponsors simply don't share data on past performance [with other sponsors]."

Even with near-perfect execution of study steps, the danger of protocol violations is still high if investigators and their teams do not get an opportunity to engage in dialogue that increases their understanding and addresses sponsor concerns.

"Protocols these days are operationally difficult to envision," Leigh continues. "We engage to identify where a trouble spot may surface."

Supplementing the prescriptive PSSV with a candid conversation during which mutual expectations can be put on the table instills confidence with the investigator and his/her staff, as well as with the study team. The prerequisite step to making a PSSV this valuable is to do one's homework and get the study team to align on what it needs to get out of the visit.

In one study, senior members of the sponsor team decided to go to several sites to walk through the data capture system with investigators and research managers. The meetings turned into full dry runs. The biggest surprise was how simply in-person discussions translated "ah-ha" insights into simple fixes, some of which avoided the unnecessary exclusion of patients. Referencing the engagement model, the research managers became constructively critical Participants in the study community. Some will settle back into an Attendee or even an Observer role, and that's okay. The sponsor hopes some keep their participation level up and that, perhaps, one or two will become Champions.

Summary

Despite the technical, procedural, and regulatory nature of the clinical research enterprise, the clinical trial is still a long-distance, long-term relationship. The energy people need to play their part to the best of their abilities over long periods of time is sustained by the trust and respect that comes with productive working relationships. Although tools and technology help, ultimately it is the creative energy of a thoughtful study team that inspires people to perform and allows every member of the study community to experience a high-performing, functional team environment. Engagement does not start at site activation, or even the first patient visit; it has to begin with the sponsor study team, long before the study starts.

Acknowledgments

Much of the content in this article is not specific to clinical research, and is based on the authors' experiences as part of the new work movement known as coworking. Credit for foundational concepts goes to Alex Hillman and Adam Teterus at Indy Hall and Tony Bacigalupo at New Work City. For additional reading, visit http://betterwork.co, http://indyhall.org, and http://nwc.co.

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Study Risk Determinations

Two of the questions the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) Investigational Device Exemption (IDE) Office commonly receives are:

- Does FDA consider my study a significant risk study, requiring an IDE?
- What is the difference in defining a significant risk device vs. a significant risk study?

Significant risk studies require both FDA and IRB approval prior to initiation of a clinical study.

Significant vs. Nonsignificant Risk Devices

A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease, or in preventing impairment to human health.[1] Examples include sutures, cardiac pacemakers, hydrocephalus shunts, dermal filler implants, and orthopedic implants.

A nonsignificant risk device does not pose a significant risk to human subjects. Examples include digital mammography, ultrasonic dental scalers, and Foley catheters. Additional examples of significant risk and nonsignificant risk devices are included in FDA's "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors on Significant Risk and Nonsignificant Risk Medical Device Studies."[2]

Significant Risk Studies

Significant risk studies require both FDA and institutional review board (IRB) approval prior to initiation of a clinical study. FDA approval is obtained by submitting an IDE application to FDA.[3] All clinical investigations of significant risk devices must have an approved IDE for a significant risk study or be exempt from the IDE regulation.[4]

Some studies of nonsignificant risk devices may be significant risk studies, depending on the study design or indication. The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. In making this determination, one should consider the nature of harm that may result from use of the device and if an additional procedure is required for the study. For example, a low-level laser used to treat pain is considered a nonsignificant risk device; but if it is used for invasive sampling, it would be considered a significant risk study.[5]

Investigations that are exempted from the IDE regulation include:[4]

- A legally marketed device when used in accordance with its labeling
- Diagnostic devices, if the sponsor complies with applicable labeling requirements[6] and if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure[7]
- Devices undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk
- Devices intended solely for veterinary use
- Devices shipped solely for research on or with laboratory animals and appropriately labeled[8]
- Custom devices, unless the device is being used to determine safety or effectiveness for commercial distribution[9]

Depending upon the nature of the investigation, studies that are exempt from the requirements of the IDE regulation may or may not be exempt from the requirements for IRB review and approval[10] and the requirements for obtaining informed consent.[11]

Nonsignificant risk device studies must follow the abbreviated requirements addressing labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion.

Nonsignificant Risk Study

A nonsignificant risk study requires IRB approval prior to initiation. Sponsors of nonsignificant risk studies are not required to submit an IDE application, and there is no need to submit progress reports to FDA. However, nonsignificant risk device studies must follow the abbreviated requirements, which address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion.[12]

Study Risk Determination

An IRB can make a determination of whether the study should be considered a significant risk or nonsignificant risk study.[13] Sponsors should present an explanation to the IRB why a study does not pose a significant risk. If the IRB disagrees and determines that the study poses a significant risk, the sponsor must report this finding to FDA within five working days.[14]

If the IRB concurs with the nonsignificant risk determination and approves the study, the sponsor can start the study, provided that the abbreviated IDE requirements given in 812.2(b) of the *Code of Federal Regulations* are met. However, FDA is the final arbiter in deciding whether a device study poses a significant or nonsignificant risk. If FDA disagrees with an IRB's nonsignificant risk decision and determines that the study poses a significant risk, the sponsor may not begin its study until FDA approves an IDE.[15]

A sponsor can also ask FDA to review the study and make a determination regarding the significant/nonsignificant risk status. This is done by submitting a no-cost pre-submission, asking FDA to make the study risk determination.[16] The specific information that is needed for a risk determination or "Pre-Submission—Study Determination Request" is as follows:

- A detailed device description (for each device, if more than one is in the study)
- The protocol for the study, including
  - A description of how the device will be used
  - A description of the population
- The sponsor's name and contact person(s), including titles, address, phone number, fax number, and e-mail address

The cover letter should state "Pre-Submission—Study Determination Request" in the reference line. Two copies should be submitted to the Document Mail Center:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

One of the copies must be electronic. More information about eCopies can be found in the eCopy Program for Medical Device Submissions Guidance.[17]

FDA Study Risk Determination Process

The pre-submission will be assigned a "Q" number. The assignment of an identification number is used as a tracking mechanism and a method of giving feedback to sponsors, and does not obligate the sponsor to submit an IDE. The sponsor will be notified via e-mail that the pre-submission was received and if there were any issues with the submitted file (e.g., inadequate number of copies, eCopy did meet the requirements, etc.).

If the review team has questions or needs additional information to make the determination, FDA may contact the sponsor prior to making a study risk determination.[18] This could include requesting information via e-mail, phone call, or teleconference. FDA may also request that the sponsor submit additional material to the Document Mail Center.

FDA intends to complete study risk determination requests within 90 days. Once the determination is made, a study determination letter will be sent to the sponsor indicating whether the study is significant risk, nonsignificant risk, exempt, or basic physiologic research. The letter may be copied and submitted to the IRB(s) with the protocol. In this case, the IRB does not need to make an independent assessment of risk; it should use FDA's determination.

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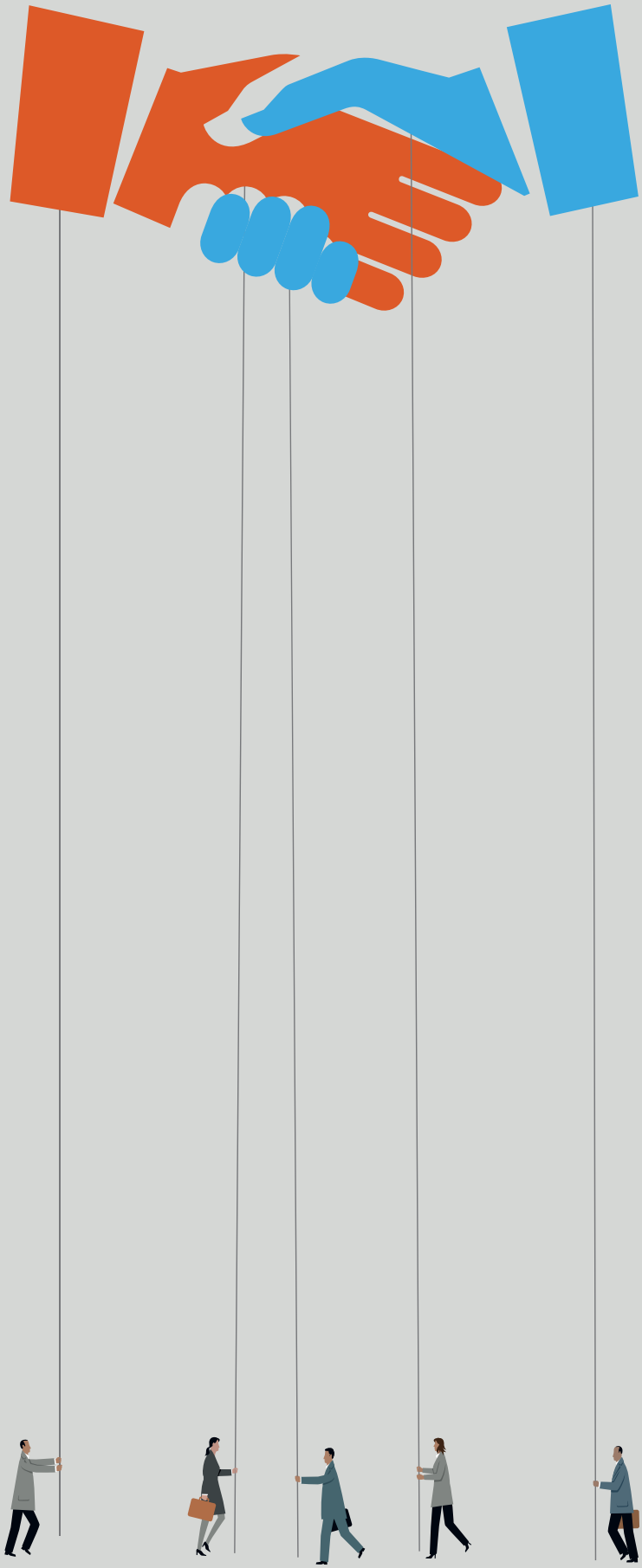


The Organizational Marriage Counseling of Sponsor-CRO Relationship Management

PEER REVIEWED

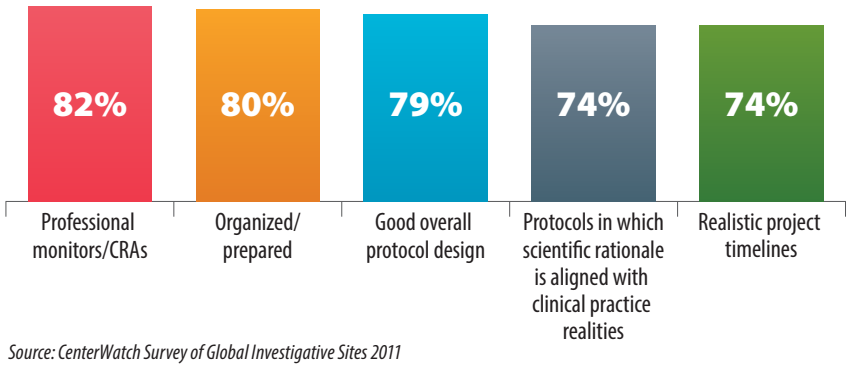
Nikki Christison, BS

[DOI: 10.14524/CR-13-00060R1.1]

Personal relationships take work, patience, and commitment. Why should work relationships be any different? If you have children, the dynamics of a relationship become even more challenging: Which parent gets to decide what is right, what limits should be set, and who has to be the enforcer? When we "marry" a sponsor to a contract research organization (CRO), we need to focus on relationship and expectation management in order to best "parent" a project; otherwise both parties can anticipate challenges and disappointments in performance. A changing regulatory climate, including new risk-based monitoring (RBM) applications, make it even more critical that we ensure consistent understanding and application of information by all.

This article focuses on managing sponsor-CRO relationships and enhancing communication between the stakeholders. A discussion of considerations in a risk-based environment is included, as well as interviews with representatives from sponsors, CROs, and niche providers on relationship challenges and solutions.

FIGURE 1. Essential Attributes to Study Success



Source: CenterWatch Survey of Global Investigative Sites 2011
CenterWatch Clinical Trials Data Library

Defining Relationship Challenges

Failed sponsor-CRO relationships reveal delayed timelines, escalated budgets due to change-in-scope activities, high turnover, frustrated sites, and, on occasion, compromised data. A series of six interviews were conducted to gather information and feedback on the challenges faced in these relationships and how to address them. Although the sample size was small, the same themes were echoed by all parties related to the most significant challenges they face. Two interviews were conducted with sponsors, three with CROs (offering all aspects of trial development and management services), and one with a CRO niche provider specializing in training.

When asked to define key sponsor-CRO relationship challenges, the sponsor representatives focused primarily on expectations, whereas the CRO representatives emphasized the need for communication.

When asked, "What is the biggest challenge you face in relationship management between sponsors and CROs," Patti Orozco-Cronin, director of clinical operations for Corcept Therapeutics (a sponsor), stated "Expectations and deliverables can change over time, in fact, often do." On the other hand, Dee Williams, project manager at Clinipace Worldwide (a CRO), stated that the biggest challenge was "establishing a satisfactory communication pattern that fits each unique sponsor-CRO team."

An examination of the importance of relationships across the industry reveals their importance at every level. Beyond the internal relationships found in any sponsor-CRO pairing, the effects of the arrangement filter down to study sites.

According to the CenterWatch Clinical Trials Data Library, "Professional and organized monitors/clinical research associates (CRAs)" were ranked higher in importance as an attribute than realistic project timelines, as illustrated in Figure 1. This seems to indicate that relationships are a critical factor in all aspects of trial management.

Illustrative Examples

The challenges as related to expectations and communication can lead to roadblocks to study execution. For example, if the expectations for ownership are not clearly defined, the results will be poorly communicated and there will be a lack of ownership for the process and desired outcome.

Consider the tracking of patient enrollment metrics; although the timelines are laid out on paper and performance metrics are regularly provided from the CRO to the sponsor, there rarely are expectations set for what the intervention plan is, who owns it, and what has to happen if performance falls behind plan. If these elements are not defined, the result is a sponsor that puts pressure on a CRO that does not have resources, time, or defined responsibility for addressing slow recruitment.

The expectations for intervention at each predefined metric time point should be addressed up front, and the path for escalation, intervention, and communication clearly defined. Thus, if enrollment is five patients behind at the end of month one, an immediate root cause analysis should be implemented and action taken to address the issue behind slow enrollment. If the CRO is only contracted to monitor sites and track metrics, it may believe it has fulfilled its obligations to provide the metrics report. The sponsor, on the other hand, may be expecting the CRO to develop an intervention regarding the poor enrollment problem. If the expectation is not defined clearly and communicated up front, all parties are left frustrated and enrollment continues to languish.

When asked to define key sponsor-CRO relationship challenges, the sponsor representatives focused primarily on expectations, whereas the CRO representatives emphasized the need for communication.

An industry push for RBM or adaptive monitoring practices, then, would cause the challenges in establishing appropriate communication and expectations to increase exponentially. How will risk factors be defined and how will the expectations for escalation and management of those identified factors be addressed when dealing with two sets of standard operating procedures if the sponsor has one set and the CRO has another?

Varying opinions on what it means to adapt monitoring practices and identify risk based on a nebulous set of guidances and industry

TABLE 1. Response to Question: Do you anticipate any additional challenges or improvements in the sponsor-CRO relationship or changes with the implementation of RBM?

CRO Specializing in Training	CRO Broad Service Provider (1)	CRO Broad Service Provider (2)	CRO Broad Service Provider (3)	Sponsor (1)	Sponsor (2)
It is my understanding that additional emphasis on site training will be important for sponsors as RBM is implemented.	I am just now implementing an RBM plan for a sponsor that has wanted RBM... but has also sent mixed messages on expectations.... So yes, I think this is another area that requires very careful communication in both developing the plan and ongoing implementation. All parties must be involved in the process and stay committed to involvement as the plan moves into place.	Use of an RBM strategy can work well if the risks applicable to the study are well defined and the appropriate risk management strategy is implemented.... All parties must manage RBM closely and adjust as necessary.	No comment	No	Yes, I anticipate that the changing regulatory environment will require a learning curve for implementation and, during that time, the standard number of mistakes will be made while taking [RBM from] concept to process is ironed out.

If the expectations for ownership are not clearly defined, the results will be poorly communicated and there will be a lack of ownership for the process and desired outcome.

opinions make it evident that the challenges are multitiered, beginning with confirming and establishing expectations for all parties in writing.

The interviewees had differing views when asked if they anticipated any additional challenges or improvements in the sponsor-CRO relationship with the implementation of RBM. The responses were mixed, from an emphasis on focusing on training to not anticipating any additional challenges. One sponsor stressed that there will be a learning curve for implementation and mistakes will be made while taking the concept to a process.

In general, the interviewees were positive about the effect that the changes will have on team relationships and that they will eventually allow project leaders to focus on the critical elements in each study. Table 1 provides a summary of the responses on the topic of RBM.

Identifying the Source of Poor Sponsor-CRO Relationships

Boris Iossel, head of operations for North America at PSI CRO, emphasized that "depending on the size and the current lifecycle stage of the sponsor company, there may be additional challenges.... The smaller sponsor or a startup may have less previous experience with clinical trials and, at the same time, would also be under extreme pressure from the investors to get things done quickly. Such a combination may result in projections and requests that may not be feasible in a real life situation." He also suggested practical and critical considerations for managing the relationship, which will be discussed later.

Late outsourcing activities (when a CRO partner is brought in once the protocol is fully developed) represent an additional challenge identified by the interviewees. The partner must work under compressed timelines without the benefit of a lot of the thinking and rationale that may have gone into the study design.

Lynn Kalinoski, program manager for Arrowhead Research Corporation (a sponsor), noted that one of the biggest challenges is "interpretation of the project assumptions and tasks and coming to clarity on roles and expectations. For example, many contracts and communications are particularly acronym heavy or company-specific, which makes review, negotiation, and implementation difficult."

The variety of issues points out the need to determine their causes and thus learn how to address them proactively. Three key factors relate to challenges in relationships: expectations, communication, and follow-through. The source of the majority of issues is not defining expectations for and from both parties; if the relationship is to be collaborative, then both the sponsor and CRO need to define expectations for each task considered in the scope of work—not just what the task is, but what should be done related to each task.

The second, and perhaps most significant, cause is poor communication. Communication pathways must be established and sponsors must allow CROs to move forward with the expertise for which they have been hired. They must also, however, allow for constant communication to ensure the expectations are being implemented clearly.

Finally, follow-through (or ownership) of tasks is critical. A CRO may not appear to "own" the study processes. However, there are several possible reasons that it has not taken ownership:

- Was the expectation for ownership clearly communicated?
- Was the CRO encouraged to develop processes to ensure early and proactive interventions for risks related to the study?
- Does the sponsor continue to remain involved and available as a resource, rather than a dictator?

- Has the CRO been discouraged or received negative feedback for trying to be proactive by a sponsor who is reluctant to let go of some of the control over the study?

All of these questions relate back to the need for clear communication and expectation setting. A CRO respondent stated, "When a CRO is contracted to work on a study, sponsor responsibility remains to provide timely approvals on documents, project plans, and processes at a minimum. All responsibilities are not abdicated!"

Fixing the Problem

Although there is rarely a one-size-fits-all solution, the tactic that appears to be the most appropriate in this case is to focus on root cause analysis and communication. This should include communicating expectations up front, establishing communication pathways for the duration of a project, and considering how (and how well) one communicates with others in the first place.

For example, when a sponsor is frustrated by the rate of turnover of monitors on a project, the approach should be to work with the CRO to identify the cause of the issue and determine how to address it as a partnership. This will require sharing information, collaborating on a solution, and following through on implementation—none of which can be done if the communication does not go both ways.

One possibility is the initial perception that a high monitor turnover is an issue with the CRO if its staff are leaving, but perhaps it is related to a specific project. Perhaps the CRAs are not receiving enough support from, or prompt response to questions addressed to, the sponsor. If the appropriate questions are not asked, the facts necessary to addressing and resolving the problem will never come to light.

As Iossel suggested, "In order to address the issues early and avoid unnecessary anxiety and unmet expectations as much as possible, more custom-tailored effort may need to be invested in gaining trust and building successful synergistic relationships between the CRO and the company. These will include open, fact-backed discussion to assess how realistic the expectations are on the side of the sponsor, understand the reasoning behind the projections that may be unrealistic, and come up with a mutual, clear understanding of what would be the best attainable scenario for the project."

When asked if there is one thing that could "fix" the relationship problem between sponsors and CROs, a CRO responder stated, "Commitment on both sides for healthy collaboration and respectful [and] direct communication when there are differences." Solutions for consideration in addressing problem relationships are listed in Table 2.

Conclusions

When it comes to optimizing clinical trial performance, sometimes we have to go back to the basics. This is particularly important in an outsourced environment that is facing many unknowns, such as how applying RBM will work in day-to-day practice.

Good communication practices can overcome many challenges in sponsor-CRO relationships. Setting clear expectations and documenting them in writing, and establishing and adhering to communication and issue escalation plans can all prevent study performance issues. When challenges do arise, taking the time to do a root cause analysis to uncover the source(s) of the problem can also ensure that any interventions will appropriately address the core cause of the problem.

Following these basics can go a long way to ensuring a successful sponsor-CRO marriage. Perhaps we should consider our marriage vows in this collaboration to be "Thou shalt respect one another and commit to communicate."

Acknowledgment

The author extends a special "thank you" to the interviewees mentioned in this article for their time and insights.

TABLE 2. Solutions for Addressing Problem Relationships

Tip	Details
1. Communicate	Communicate throughout the project, not just when there are problems. Communication pathways should be identified prior to the project start in the Scope of Work, Project Plans, Monitoring Plans, Data Management Plans, etc.
2. Identify	Identify challenges before they become issues through routine communication. Share concerns and possible study risks. Conduct a root cause analysis to identify the source of the problem.
3. Escalate	As an issue and the source of the problem are identified, escalate the information to ensure that all parties are aware of potential challenges and that proactive support can be provided from senior management in both organizations.
4. Commit	Commit as a joint team to resolve issues collaboratively and communicate "lessons learned" freely to ensure preventative measures are followed to avoid future issues.
5. Resolve	Follow each problem through to resolution on both sides of the partnership. Commit to ensuring adequate resolution from both sides vs. delegating all resolution responsibility to one party.

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An Interview with Susan H. Warne, LVN, CCRC

It is my pleasure to share this issue's Careers—Passing it On interview with a longtime colleague: ACRP advocate and volunteer, **Susan H. Warne, LVN, CCRC.** Susan is a strategic site relationships manager with Quintiles, although she has held multiple roles during her extensive clinical research career.

Q. How did you first become interested in clinical research, and can you describe a little bit about the path you took to get involved with your clinical research career?

A. I initially became interested in clinical research while working as an office nurse for a practicing physician and principal investigator who also ran a clinical research center. Since I was always looking for a challenge, the clinical research process was of interest to me. I was eventually able to take advantage of an opening for a clinical research coordinator (CRC) for that same physician/investigator.

Q. Can you tell us a bit more about where you started and the different types of roles you've held?

A. Initially, I worked as a CRC, mentored by my colleagues. I was promoted to operations manager for a short period of time, and was responsible for the day-to-day operations of the clinical research center.

When two of the investigators from the site, along with two additional investigators, launched a niche-focused site management organization (SMO), they hired me as their initial project manager. I remained with the SMO for eight years and held a number of positions, including project director and, ultimately, vice president of strategic services, working on proposals, budgets, and contracts for the SMO member sites.

In each role, I continued to stretch myself a bit more and take on new and challenging responsibilities. I have also worked as a project manager for a patient recruitment provider, from which I gained additional valuable experience. My current position as a strategic site relationships manager for a major contract research organization was made possible by the culmination of experiences across my 19-year career, which has focused on many aspects of patient- and site-related clinical research activities.

Networking, volunteering, and developing relationships with ACRP colleagues have greatly enhanced my career choice options.

In each role, I continued to stretch myself a bit more and take on new and challenging responsibilities.

Q. When did you first get involved in ACRP, and what type of benefits have you reaped from being a member?

A. I first became involved with ACRP as a result of applying for and taking the CRC certification exam. I have remained a member ever since, as ACRP is the professional organization for the clinical research industry—providing access to education, a resource for knowledge, and an opportunity to network with like-minded professionals. Networking, volunteering, and developing relationships with ACRP colleagues have greatly enhanced my career choice options.

Q. Since your career has spanned many years and you have no doubt seen many changes, what is the most significant change (or top changes) you have seen? How do you think these changes have affected the industry, either positively or negatively?

A. The complexity of protocols resulting in additional responsibilities for all members of the clinical research team is by far one of the greatest challenges I have observed. More complex protocols require greater knowledge (and access to that knowledge) to maintain safe, ethical, and quality clinical research conduct.

I am not sure whether this is a negative or positive—perhaps both. A negative would be more complex trials requiring additional work and an increasingly skilled workforce. The positive is gaining access to more robust data and a better understanding of the treatments being developed.

Q. What advice do you have for clinical research professionals, in terms of how to further advance their careers?

A. Stay connected! If not certified, become certified and maintain certification. Volunteer with your professional organization and network with other clinical research professionals. Challenge and stretch yourself to periodically get out of your comfort zone to gain valuable experience that can be leveraged for future positions.

Q. As you think about the future generation of clinical research professionals, what three "lessons learned" would you like to share?

A. First, don't be afraid to start at the bottom or take lateral moves; they may offer opportunities to get exposure to multiple areas of the clinical research process.

Second, keep an open mind, and embrace change; clinical research is dynamic in nature.

Finally, always keep in mind our focus as research professionals—working to find better, safer, and more effective treatments for patients.

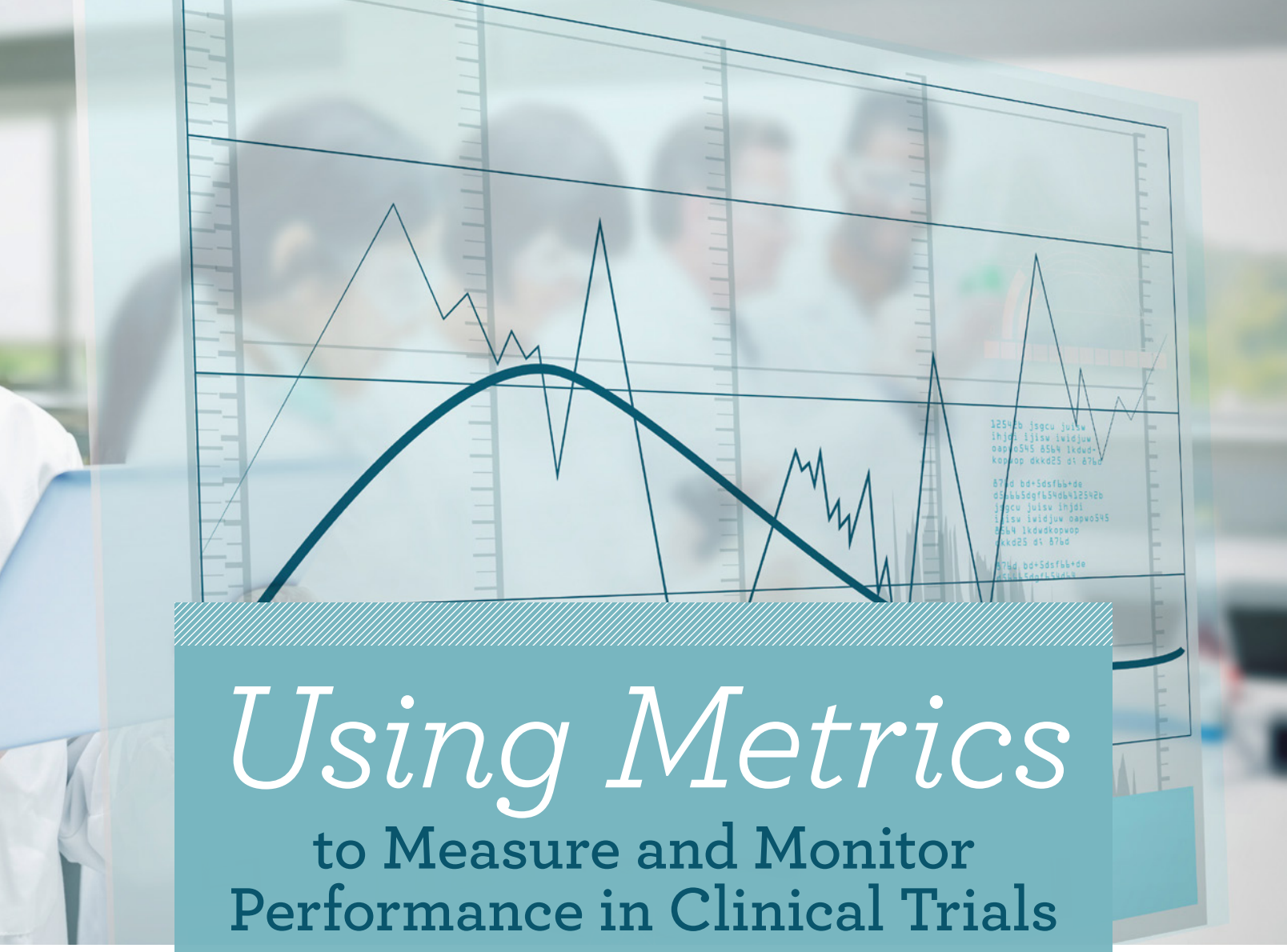
Q. Are there any closing thoughts you would like to share?

A. However long you have been a part of it, always remember that clinical research is not a "job," but a commitment to a rewarding profession.

Susan, thank you for sharing your perspectives with us. From patient care provider and nurse to strategic site relationships manager, you have clearly followed your own advice to continuously evolve in your professional career. We'll all be interested to see how you "stretch" yourself into further roles in the years to come.

Beth D. Harper, MBA, is the president of Clinical Performance Partners, Inc., and a member of the ACRP Editorial Advisory Board. She can be reached at bharper@clinicalperformancepartners.com.

Challenge and stretch yourself to periodically get out of your comfort zone to gain valuable experience that can be leveraged for future positions.



Using Metrics

to Measure and Monitor Performance in Clinical Trials

PEER REVIEWED | Randy Drew Krauss, PhD

[DOI: 10.14524/CR-13-00054R1.1]

These days, more and more companies are turning to performance metrics. If used appropriately, metrics can be used to manage expectations, improve planning, identify issues before they become problems, and/or improve performance (people, resources, process) as needed.

Even as an industry that bases its success on data, the clinical research enterprise struggles to identify and use operational metrics appropriately. There is never a shortage of things to measure. In fact, if you asked a group of colleagues to hold a meeting to identify new metrics, they could fill a wall with sticky notes, each with a metric. The result is that more metrics are implemented than necessary. By doing this, organizations often lose sight of why they are measuring something and how to use metrics to monitor and improve performance.

A better place to start is by asking what is important to the organization. Some companies have adopted a Balanced Scorecard approach to aligning business activities with the vision and strategy of the organization. Others are using methodologies such as Lean Six Sigma[1,2] to focus on the elimination of waste within various processes in the organization.

Whatever the method, once this is done, you are in a better position to identify appropriate metrics for your purposes. There are different types of metrics: cycle time, timeliness, quality, and efficiency/cost. A single metric will not tell you everything you need to know about a given process; you may need additional metric(s). They may provide insight into your performance, but they will not answer all the questions and/or provide a solution.

Enter the Stakeholders

Implementing metrics is often dependent on two types of stakeholders—"data providers" and "data consumers"—working together. Data providers provide the data that go into calculating the metric, and data consumers want to use the data and often know how they would like to view them. Sometimes, individuals can wear both hats.

The stakeholders must work together on four components:

- a clear understanding of what is expected (definitions),
- access to the required data (preferably centralized to avoid ambiguity and duplication),
- assurance that the data are complete and accurate, and
- governance (i.e., when can you change the baseline with respect to measuring performance, such as planned completion date or planned number of patients).

If we were allowed to change the baselines, we might always look perfect. Although the data consumers usually expect data very soon after identifying the metric, these components are often challenging and may take time to resolve. Ultimately, they could prevent you from successfully implementing a metric.

How do you know if you are successful or performing as expected? Every metric must have a plan or goal against which to be measured. Without it, you will not know how you are performing.

When available, historical data can be used to help set a performance goal. If your past on-time performance in terms of reaching database lock is 40%, then setting a goal of 80% may not be reasonable without an understanding of what is driving the delays. That being said, you have to set reasonable goals; goals that would pass the "red face" test with your management team or regulators. A performance goal should be a bit of a stretch, and can change over time as your processes improve.

Activation/Enrollment Metrics

With respect to clinical operations, enrollment and monitoring are highly visible and critical to the success of a trial. For enrollment, the most critical question is: Will we or did we enroll the last patient on time (plus or minus x days to be considered on time)? Although the cycle time is important in planning, your stakeholders will want to know if you completed enrollment on time.

An analogy here would be that of a house builder. The builder can tell you that it will take six months to build the house (cycle time), but what you really care about is on what day you can move in or, if you moved in, did you move on the date promised (timeliness). If the builder can say that 80% of the new homeowners move in on the day promised, you will feel pretty good about your chances. If it was 40%, you won't have much confidence.

To deliver the last patient on time, you must activate sites and enroll patients according to a plan (see Table 1).[3] Thus, there are three key metrics involved:

- Last patient enrolled on time
- Site activation vs. plan (Figure 1)
- Patient enrollment vs. plan (Figure 1)

As an aggregate (and depending on whether or not a majority of your studies are of the same size), each of these metrics could provide insight into your activation and enrollment processes. By study, they are leading indicators as to whether or not you will reach your last patient enrolled on-time milestone, as they will help identify areas of concern before they are issues. A mitigation plan could then be put into place to ensure you can deliver on the date promised.

TABLE 1. Some Different Types of Trial Metrics

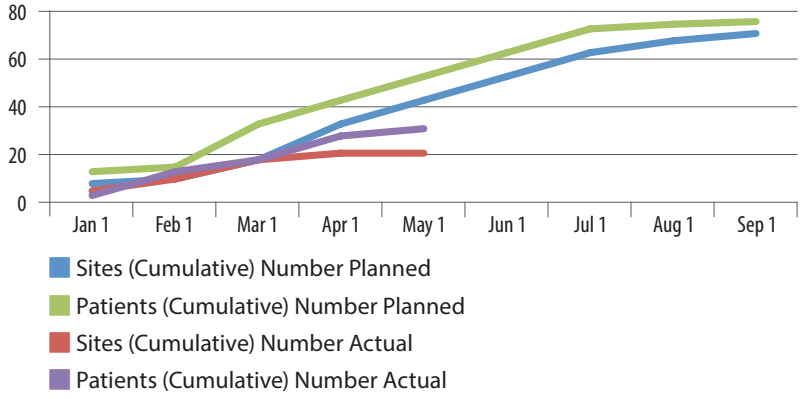
Activation/Enrollment Metrics	Monitoring Metrics
Last patient enrolled on time	Monitoring vs. plan
Site activation vs. plan	Trip reports submitted on time
Patient enrollment vs. plan	Action items closed within x days
Site productivity	% data monitored within x days

For example, if you have activated only 25% (and the target is 50%) of your planned sites for a given month(s), you will not enroll patients at the planned rate. This will ultimately cause you to miss the last-patient-enrolled date.

Different data consumers will likely have different needs with respect to the level of detail. These metrics could be available at different levels or cuts (for example, study, country, and site, or therapeutic area, phase, and sourcing type). Moreover, activating and enrolling patients earlier or later than planned may not affect timelines alone, but could have significant side effects on availability of resources and cost.

Even as an industry that bases its success on data, the clinical research enterprise struggles to identify and use operational metrics appropriately.

FIGURE 1. Site Activation/Enrollment Over Time



Since metrics often lead to more questions, organizations often create more metrics to answer those questions. Additional metrics to support key performance indicators may be steps in a process that might be rate-limiting. For site activation, that may be preparation or submission of regulatory documents, site contracts, or institutional review board applications. Sometimes, though, it takes old-fashioned investigating to understand the problem.

Site productivity is another important metric that can be used as a leading or lagging indicator (see Table 1). The Tufts Center for the Study of Drug Development[4] reported that 37% of sites miss enrollment targets, with an additional 10% failing to enroll a single patient. As a lagging indicator, in aggregate, productivity can provide insight into the site selection process, but at the site level, it is an indicator of whether or not a site reaches its enrollment goal.

With this information, contingency plans can be put into place for the site(s), or it can be closed. It may be more costly to keep a site with a patient or two open instead of closing it. For future studies, the sponsor could increase or decrease the goal based on past performance, or decide not to use the site at all.

Monitoring Metrics

Site monitoring is another critical component in the execution of a clinical trial. Sites are monitored to:

- protect human subjects,
- ensure data integrity, and
- encourage adherence to the protocol.

Every study has a monitoring plan (regardless of whether it is traditionally monitored or risk-based), which stipulates how the study is going to be monitored. Failure to monitor as stated in the plan can have significant consequences in terms of the reactions of regulatory authorities.

Implementing and maintaining metrics related to adherence to the monitoring plan is often done manually (see Table 1), as standard clinical trial management systems (CTMS) often do not capture the nuances of different plans, given the uniqueness of every study. This may change as risk-based monitoring is implemented in more studies.

There is usually a standard operating procedure stating the timeframe in which trip reports should be submitted and approved after a monitoring visit. Measuring the time it takes trip reports to be submitted and approved against this goal is straightforward. Additional cuts by report type, country, therapeutic area, monitor, or overall vendor may provide some insight with respect to areas of concern.

Often, a monitoring visit will result in action items, which must be reviewed and closed in a reasonable period of time. Once in a CTMS, such items can get lost in vast amounts of data; however, not completing them in a timely manner puts the study at risk.

A leading indicator of a site's ability to lock the database on time is ensuring that data are monitored and queries closed in a timely manner. Tracking these will provide site staff with areas of concern, perhaps including resource issues, and allow them to manage expectations, if necessary.

> The most important part of any metrics program is not reporting the metrics, but how organizations respond to them.

Conclusion

A sponsor expects a trial to be completed in a timely, cost-effective manner while ensuring high quality. Delivering milestones on time (timeliness; i.e., last patient enrolled) gives site staff confidence in their abilities to plan and adjust as they execute, and gives the sponsor confidence in the site's capabilities.

Measuring a site's ability to activate studies and enroll patients according to plan will be a leading indicator of its wherewithal to enroll that last patient when the plan said it would happen. Knowing what to measure and how to use it is essential for any metrics program.

All too often, organizations will periodically report their metrics and stop there. The most important part of any metrics program is not reporting the metrics, but how organizations respond to them. This will provide critical insight into an organization's or site's processes and whether process, resource, or individual/team performance issues exist. Staff and stakeholders will then know whether the anecdotal stories at the water cooler are accurate, and when to be proud of the organization's or site's accomplishments.

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