Trends in Clinical Trial Site Selection and Patient Recruitment
Competition for clinical trial sites and participants has never been stronger. The number of trials registered at clinicaltrials.gov nearly tripled from 2000 to 2014. Along with an escalating number of trials, drug and medical device developers face increasing complex trial protocols, fierce competition for patients in certain therapeutic areas, an expanded global trial landscape, and increased regulatory requirements. As a result, the cost and time needed to secure well-qualified sites and enroll patients has soared.

Clearly, setting up clinical trials can be daunting for drug and medical device developers. This challenging marketplace is driving sponsors and contract research organizations (CROs) to find new solutions to lower costs and improve trial efficiency in order to bring innovative new drugs and medical devices to market.

The essential requirements for making site selection and recruitment more efficient are a combination of selecting high-quality, high-performing sites on a global landscape, identifying efficiencies, and optimizing use of the latest technology – including e-clinical technologies that provide real-time access to data, as well as Web-based tools and social and mobile media. As technology plays an expanding role in clinical trials, sponsors are increasingly partnering with digital CROs to help them make informed, data-driven decisions and reduce trial costs and time. This paper reviews the current challenges of clinical trial set-up and the essential tools needed to speed site activation and reduce costs.

**Trends in Clinical Trials**

Today, an increasing number of small, virtual and biotech sponsors are conducting smaller-scale trials based on new discoveries for potentially innovative new drugs. Larger sponsors are focused on extending the lifecycle of legacy drugs through new indications, over-the-counter versions, and new drug delivery systems.
The clinical stage of drug and device development is time-consuming and costly, beginning with a small group of about 20 people (Phase I) to test side effects with increasing doses and ending with larger trials of about 5,000 people (Phase III) to test efficacy. Companies may opt for an additional trial (Phase IV) after a drug is approved and marketed, enrolling several hundred or several thousand volunteers.

With a single clinical trial costing more than $100 million, it is not surprising that the expense of successfully bringing a single drug to market has risen to between $350 million and $1.2 billion. Over the last decade, companies that have brought four to 13 drugs to market have seen the costs soaring to more than $5 billion.

Site Selection Considerations and Challenges

For Phase I or II trials, it is advisable to build a relationship with high-level academic sites known for their expertise, thought leadership, and history of breakthrough models in various therapeutic specialties. Moving into Phases II and III, most sponsors and CROs cast a wider net for site selection based on the study protocol, economics, and the site’s experience in successfully conducted trials in the same disease area. Site selection may also depend on the location of a large population with the condition being studied, availability of specialists in a narrow disease specialty, and access to testing laboratories or specialized equipment.

Sponsors and CROs are competing for high-performing sites in the most common disease areas of clinical research. Currently, according to The Center for Information and Study on Clinical Research Participation, the highest number of trials are for oncology and immunomodulators, central nervous system, anti-infectives, cardiovascular, and diabetes treatments. Finding sites with a demonstrated track record of good performance in trials similar to your study and site personnel with strong credentials increase the probability of effective recruitment and a successful trial. Another challenge of site selection is identifying the site’s correct qualifications. Many new technology tools are now available for sites to disclose their qualifications and credentials to sponsors and CROs.
Site Selection Solutions: Securing High-Performing Sites

Actions at the Outset

Before starting a search for qualified sites, it is essential to have a detailed, comprehensive study design that clearly specifies the patient population, investigator specialties, personnel and equipment required for the trial. When considering a site, evaluate both its productivity in past clinical trials and real-time feasibility for a new trial. Taking time to ensure that selected sites have the appropriate qualifications, staff motivation, patient population, infrastructure, and support at the outset will help secure consistent, high-quality enrollment during the course of your trial.

To identify the best-performing sites that align with your study protocol, begin by searching your internal database, external databases and websites and obtaining recommendations. Maintaining positive relationships with high-quality sites will facilitate site selection. For investigator recruitment, many niche databases are available.

Industry networking is becoming more valuable in site selection, with resources such as LinkedIn. Social media, such as LinkedIn, is playing an increasing role in site identification, enabling easier access to colleagues and peers, and communicating with them following industry meetings.

Global Trial Considerations

When considering global sites, it is important to select regions where the disease to be studied is prevalent and to consider the standard of care in each country. Learn about conducting trials in a given region as local laws and cultures can have a significant impact on the success of study set-up and enrollment. Choosing a site in a country that has a national healthcare system can be advantageous for fiscal benefits, therapeutic need of the patient population, historical relevance with the compound’s development, or the country’s regulatory environment.

According to The Center for Information and Study on Clinical Research Participation, the highest number of trials are for oncology and immunomodulators, central nervous system, anti-infectives, cardiovascular, and diabetes treatments.

Industry consortiums, conferences and other industry tools can also be valuable for site selection. They provide opportunities to learn about sites from colleagues and find out firsthand about industry advances. For example, as a result of a recent industry consortium, a new Drug Information Association (DIA) Trial Master File (TMF) Reference Model was released, providing a single, unified interpretation of the regulations and best practices regarding the content of a TMF.
Also important is avoiding regions already saturated with clinical trials. In global trials, CROs have seen a shift to fewer trials in India, somewhat improved conditions in China, and a rise in CRO services in Japan in 2013 as a result of a shortened regulatory applications process.\footnote{4}

**Gaining Efficiencies**

Sponsors and CROs are scaling back the number of investigative sites they operate and the number of countries where they locate trials, which helps reduce the costs of trial set-up. Actively working with sites at start-up and offering support during enrollment, as well as providing the right tools and regulatory documents in an organized manner, makes trial set-up far more efficient.

In the United States, consider alternatives to major medical centers. Community-based settings can be very competitive in their ability to enroll patients.

**Challenges in Patient Recruitment**

While enrolling patients is vital to the success of a clinical trial, it is also a major source of research expense and delays. The average cost to develop a new drug is in the billions, and a significant contributing factor is patient enrollment. A typical Phase III clinical trial takes nine months to complete enrollment and can cost up to $86 million.\footnote{5} As the time to reach full enrollment increases, the trial lasts longer and the cost of maintaining and staffing clinical sites rises. One study showed that between 2008 and 2011, the cost for a patient in a Phase I trial went from $15,000 to over $20,000. For Phase II, that cost rose from $20,000 to $25,000, and for Phase III it rose from $25,000 to $47,000. The smallest increase occurred in Phase IV, where costs rose from $13,000 to $17,000.\footnote{6}

Patient recruitment is also where most delays in clinical trials occur, incurring huge costs and the loss of potential sales. According to Applied Clinical Trials, 86 percent of trials experience delays, and CenterWatch reports that 81 percent of these delays are one to six months in length, while another 5 percent are even longer.\footnote{7} Clinical trials typically last 42 percent longer than expected in Phase I, 31 percent longer in Phase II, and 30 percent beyond planned deadlines in Phase III – all because of recruitment delays. Each day a drug is delayed from market, sponsors lose up to $8 million.\footnote{8}

Recruitment delays can also compound costs by delaying the time to product approval, often decreasing the period of exclusivity post-launch. Further, slow enrollment can lead to waning patient and site staff interest, increased staff turnover, and possible abandonment of a promising treatment.

![Figure 5. Rising Cost of a Patient in a Clinical Trial\footnote{6}](image-url.com)

<table>
<thead>
<tr>
<th>Phase</th>
<th>2008</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$15,000</td>
<td>$20,000</td>
</tr>
<tr>
<td>II</td>
<td>$20,000</td>
<td>$25,000</td>
</tr>
<tr>
<td>III</td>
<td>$25,000</td>
<td>$47,000</td>
</tr>
<tr>
<td>IV</td>
<td>$13,000</td>
<td>$17,000</td>
</tr>
</tbody>
</table>

\[^{5}\] A typical Phase III clinical trial takes nine months to complete enrollment & can cost up to $86 million.\footnote{5}
Patient barriers to trial participation in the U.S. include lack of health insurance. Another barrier is committing to additional evaluations, therapies and clinic visits beyond the normal course of treatment, which can be burdensome for older and very ill patients and their caregivers. Also, many people have negative perceptions about clinical trials, feeling trials are too risky, they will receive a placebo, or that trials are for rare or unknown diseases or only for those who have failed with other treatments. More complicated protocols create additional barriers to patient participation, increasing the time it takes to fully enroll a trial. In addition, certain insurers only cover participation in studies for treatment efficacy.

Minimal efforts by healthcare professionals to recruit subjects can be due to limited information they have on available trials and how to access them. They may also be unaware of the trial design and reporting requirements, or concerned about loss of control over their patients. Among other reasons for trial delay is that in global trials, not all sites will start enrolling patients at the same time or rate mainly because of differences in regulatory requirements. Also, more-specific, sophisticated medicines, such as dual-mechanism treatments and personalized medicines, are making it more difficult to find qualified patients after trial initiation to enroll the first patient. Increasingly, sponsors and CROs start looking into patient recruitment at the onset of the trial launch, rather than waiting for investigators to become involved. These parallel efforts of recruitment and site start-up can speed the enrollment process, improving the overall trial timeline.

As trial recruitment shifts to a more patient-centric model, drug and device developers identify several study centers with the potential to participate in their trial and complete initial regulatory documentation, but do not activate a site until an eligible patient is identified. When a site is activated, it generally enrolls subjects within a few days. This model channels important resources to productive sites and considers recruitment earlier, achieving significant gains in efficiency.

### Recruitment Tactics
Choosing a site with a large patient population that aligns with the study protocol will significantly facilitate patient recruitment. Depending on the trial protocol, standard but still viable ways to recruit patients include advertising in traditional media, and direct communication to patients by investigators and their staff, by the area medical community, and by site personnel (such as hospital marketing staff). Some physicians offer seminars to educate patients about clinical trials.

### Figure 6. Length of Trial Delays Due to Patient Recruitment

- **PHASE I**: 42%
- **PHASE II**: 30%
- **PHASE III**: 31%

Some sites may never enroll a single patient or take months after trial initiation to enroll the first patient. Increasingly, sponsors and CROs start looking into patient recruitment at the onset of the trial launch, rather than waiting for investigators to become involved. These parallel efforts of recruitment and site start-up can speed the enrollment process, improving the overall trial timeline.

### Improving Recruitment Efficiency

#### From Site-Centric to Patient-Centric
In a traditional model, patient recruitment is not considered until after research sites and investigators have been identified and prepared and all research documents are collected – a time-consuming, costly process. Moreover, some sites may never enroll a single patient or take months

---

**from clinipace.com**
websites and online clinical trial registries such as clinicaltrials.gov, a practice now required on informed consent forms.

Participating in health-focused online social networks, formed around specific medical conditions, can be very productive, directly reaching your target audience. Online patient communities, such as patientslikeeme.com, are formed around websites designed to allow patients with similar diseases to interact with one another through chats, blogs, bulletin boards and email. Since participants proactively choose to participate in disease-specific social networks to gain information about their condition and learn about new treatments, they are more likely to act upon messages received through the network than through advertising and be more motivated to enroll in a trial. Sponsors and CROs can then quickly refer patients to investigative sites.

Keep in mind that web access in some parts of the world is sparse, and some patient populations are better suited for more traditional recruitment techniques. Also, more-critical IRBs are skeptical about newer media and may have HIPPA concerns.

Multiple methods are used today to recruit patients, combining traditional tactics with an escalating adoption of newer media forms. Media outreach may include a mix of traditional advertising, direct-response mailings, and public relations, as well as online campaigns, text messages, and use of social and mobile media. Direct-to-patient programs that deliver targeted messages to prequalified patients through digital and social media channels can achieve significant gains in efficiency. Looking forward, the use of newer media is expected to become increasingly adopted to bolster recruitment efforts.

Tapping Technology
Technology plays a key role in patient recruitment. It can communicate trial information to people in a healthcare system. For example, an Intranet site can be used to house study details and their inclusion and exclusion criteria. Potential patients can be identified upon registration or check-in by linking ICD-9 codes to the key inclusion criteria or through the pharmacy when medicines in the study disease area are ordered. Internet-based sources are another efficient, low-cost approach to recruitment. Common techniques include posting studies on site
Social Media
Increasingly, organizations are turning to social media to bolster patient enrollment. This highly targeted, low-cost, flexible media offers opportunities to share clinical trial information with patients in the therapeutic area of your study. Social media enables online interactions between individuals who share common interests, facilitated by online networking websites such as Facebook and LinkedIn, microblogging platforms such as Twitter, video-sharing sites like YouTube, as well as blogs, online bulletin boards and e-forums.

Social media can educate potential patients about the value of clinical research and encourage them to participate in studies. Social media channels can also provide a good opportunity to spread awareness of specific clinical trials and encourage enrollment. In many cases, information delivered through social media reaches the family or caregivers of potential patients. But this newer media form also presents challenges in terms of privacy and HIPPA concerns as well as patient accessibility.

Mobile Devices
Along with social media, mobile technologies are increasingly being used for clinical trial recruitment and retention. The use of these technologies for specific studies and opt-in databases can potentially provide patients with access to studies they would not otherwise know about.

Clinical trials have not yet capitalized on smartphones or tablets, but these devices could be used to disseminate information to patients or capture information from them. For example, tablet applications could be used to clarify processes in trials, administer informed consent, and define words in consent forms. As with social media, mobile technology offers abundant opportunities but few current solutions. Success using the web for education and support has been limited primarily to disease states with strong advocacy groups.

Other Trends Impacting Trials
Among the latest industry trends impacting trials is adaptive trial designs, which use accumulating data to decide how to modify aspects of the study as it continues. Changes are planned in advance rather than on an ad hoc basis. Drug and device developers are forging partnerships with site personnel rather than dictating the protocol design. The flexibility of adaptive trial designs can lead to launching trials with fewer patients, and allows sites to participate in trial design to best adapt to their patient population and areas of expertise. Working as partners by allowing information to be shared in a central location and getting peer feedback on what is working or not working can streamline trials, improve protocol compliance and help achieve enrollment goals.

In addition, as the Affordable Care Act unrolls, the industry is optimistic that more patients who cannot currently afford medical treatments and lack health insurance will participate in clinical trials. Many changes are anticipated, especially relating to the standard of care, costing and insurance reimbursement.

Figure 9. Tapping Mobile Devices for Patient Recruitment

Tablet apps can be used to:
- Clarify processes in trials
- Administer informed consent
- Define words in consent forms
Conclusion

On the future field of clinical trials, technology will be the game changer. As competition for securing sites and subjects for clinical trials intensifies, technology will play an increasingly critical role in making trial set-up more efficient at the lowest cost possible. Enhanced trial designs, the availability of data using the latest technology, and the application of the right technologies are significant drivers of improved site performance and efficiency. As advances in technology soar, it will continue to enable smarter, more targeted site selection and recruitment of patients and investigators, utilizing data to identify investigators with the right skills and access to study patient populations. And by selecting the right sites, investigators and more targeted patients, clinical trials can launch more quickly and cost-effectively, bringing innovative new drugs to patients.

Author Bios

Steven Thayer
Global Manager, Site Management Services, Clinipace Worldwide
Steven has been managing clinical trial sites with Clinipace Worldwide, and formerly Paragon Biomedical, for over 15 years. Prior to Clinipace, Steven served as a facilities administrator with Private Healthcare Systems. He is based in Orange County, California.

Joanna Vandeveld
Sr. Manager, Global Site Management Services, Clinipace Worldwide
As senior manager of the Global Site Management Services group, Joanna is responsible for coordinating the allocation of SMS resources, and the delivery and tracking of timely and on-budget SMS project services for clinical trial client. Joanna has been in site management for over 13 years, and is based in Irvine, California.
References


