Patient recruitment: the costly and growing bottleneck in drug development

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The recruitment of qualified patients to participate in clinical trials continues to be a complex, competitive and costly endeavor and, more often than not, one that significantly delays the submission of new drug applications (NDAs). Within the clinical trials industry, it is a well-known fact that at least 80% of trials fail to meet their enrollment deadlines, significantly contributing to a potential cumulative loss of US$1.3 million in sales per day for a given drug candidate [1]. As research flourishes with new drug candidates, the pharmaceutical and device industries face a crucial shortage of essential and qualified patients to participate in their trials. Clinical trials consume a large valuable proportion of a patented drug's life span, which is a big problem for an industry that has an estimated 4360 new drug products in the pipeline, all of which require successful clinical trials for regulatory approval [2].

Genomic and proteomics research are said to be leading a scientific revolution which, in turn, increases the current industry prognostications of bringing new chemical entities (NCEs) from an average of 1–2 a year to at least 4–6 annually. An industry analysis in 2000 reported that gene research will create a wave of drug targets that will eventually flow into clinical development and put a serious strain on the trial system, especially if the current system continues with a void of efficiency-generating information technology [3]. Moreover, pharmacogenomics will present unprecedented challenges in patient recruitment for clinical trials, because requirements for study entry will be greatly narrowed and the resulting study population will be smaller than is currently seen.

Another current challenge is evident in that 60% of studies now contain a global component [4]. Although global patient recruitment is a growing trend, it is fragmented and fraught with cultural differences, multinational regulations, language barriers and customs. Finally, clinical trials are costly undertakings. In 2000, total spending for clinical trials from both industry and the National Institutes of Health (NIH) was reportedly US$4.3 billion, with 76% of the total (estimated US$2.9 billion) coming from pharmaceutical companies [5]. The expenditure for clinical development in Phase I–IV trials for 2001 are estimated at US$8.3 billion [PhRMA (Pharmaceutical Manufacturing Association), CenterWatch (Boston, MA, USA)].

Methods in patient recruitment – then and now

Traditionally, the pharmaceutical industry has relied on investigational sites in their specific geographical areas to recruit the required study patients. Historically, most patients who participated in clinical trials came from within the medical practices of their primary care physicians; this is still true for non-US clinical trials. A mere 15 years ago, academic investigators in large institutions performed most of the clinical trials. The primary motivations for conducting clinical research were for altruistic and scientific accomplishments. Pharmaceutical sponsors desired to have experienced 'thought leaders' conduct and publish their pivotal studies. However, as a complex and unpopular managed healthcare system has taken over in the USA and elsewhere, and physician practices have become smaller and administratively burdensome, it has become increasingly difficult to find the adequate numbers of patients for clinical trials in academic and private medical practices. As patients are increasingly on the move from one insurance plan to another and, thus, do not stay with one physician for long, it can be difficult to find and track patients interested in, or who know about, clinical trials. Contrary to recent media reports, although financial reward has grown as a motivating factor for conducting clinical trials, most investigators remain primarily motivated by scientific reasons and improved patient care [6].

Complicating the recruitment process is the fact that study sponsors routinely underestimate the costs and time required for patient recruitment, resulting in 'crisis recruitment' and even further increasing the costs of their clinical trial. All too often, the process and selection of contracting the right investigators is hastily done and not well planned. This affects directly the success or failure of patient recruitment for the entire project. Today, a sponsoring company must be prepared to fund multifaceted and comprehensive recruitment campaigns, help the sites manage this process and give realistic reimbursement to the sites for successful results. For competent sites, experience has taught us that the amount of funding for patient recruitment equates directly to the speed and success of patient enrollment. Often, the

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investigational site has to pay for patient recruitment services that are not adequately covered in the budget and ends up 'cash poor' for completing the study, therefore, jeopardizing the entire program.

The challenge of reaching patients

As the competition to get patients to enroll in clinical trials escalates, so does the need for experienced clinical investigators who can find qualified patients to enroll in the studies. By 2005, it is predicted that there will not be enough clinical investigators to handle the number of drugs in clinical development. CenterWatch estimates that there could be as much as a 15% investigator shortfall in the next five years [6]. Currently, it is estimated that the vast majority of clinical trials – 80% – are conducted by only ~20% of experienced physicians [6]. These staggering statistics underscore the crucial need to have more experienced physicians participating as investigators; clearly, without this, there will be a dearth of patients for not only the current numbers of studies but also for the predicted increase in the number of trials.

As the shortage of qualified investigators needed for the pivotal Phase II and III studies increases, a second confounding factor is the difficulty of reaching patient volunteers who are drug 'naive' or not currently taking an effective prescription drug therapy. In addition, many patients might be unwilling to stop effective current therapy to go on an investigational drug. A third confounding issue is the current media negativity towards clinical trials [7]. Although the incidence of investigator fraud and mistakes are low, the media has consistently sensationalized incidences over the past two years without balancing the numerous positive benefits of clinical research, making potential study patients much more fearful and skeptical of volunteering for studies. Together, these factors create an increasingly challenging environment for the successful and timely completion of essential clinical trials.

Over the past decade, as the number of studies requiring patient volunteers has increased, the need to find patients outside of medical practices has become evident. One method that has failed was to appeal to non-investigator physicians to refer their patients to investigational sites where studies were being conducted. This continues to fail primarily for three reasons: (1) practicing physicians do not want to potentially 'lose' their patients to another physician; (2) physicians have no real incentive to refer patients outside of their practices; and (3) most practicing physicians are not aware or educated regarding ongoing clinical trials that are available to their patients. In the early 1980s, public appeal through newspaper adverts was successful until the local medical markets became competitive as academic institutions, independent physicians and dedicated clinical trial sites competed for patients in the same geographical areas. Although print advertising is still used with relative success today, radio and television advertising has become common because it reaches an even greater audience. The 'market' for recruiting qualified patients has become more than a tiny, start-up industry; it is now a large and profitable business arena in which many different players are currently engaged.

Indeed, the USA has seen growing demand for national patient recruitment services, and many companies have emerged to fulfill this requirement. Most probably, the demand for organized, centralized patient recruitment will also grow globally, not only because of changing regulations that enable companies to file common documents but also because of a newly emerging era of direct-to-consumer advertising in Europe. To date, direct-to-consumer advertising has not been a dominant tool for recruiting clinical trial patients in Europe. Rather, recruitment efforts have largely emanated from academic centers and primary care physicians. Because of differences in cultures, local and country regulations, currency exchanges and fluctuations, attitudes, language, training and experience, it will take longer for direct-to-consumer advertising for patients to become widespread in Europe. However, the climate is ripe for change, with European countries – especially the UK – endeavoring to follow the US Good Clinical Practices (GCPs) as closely as possible.

Make no mistake – patient recruitment is a business

Although there is no hard data on what is spent in total on patient recruitment, it would not be unreasonable to speculate, by extrapolating from clinical site budgets, that spending in the low billion-dollar range could be spent on patient recruitment worldwide. With some pharmaceutical companies paying US$250,000 or more for 20 qualified patients for a difficult-to-enroll study, there is an array of new players and traditional ones with purported new strategies attempting to gain a share of the recruitment market. Ironically, the academic centers, where important research studies were most often placed in the past, are unfavorably looked upon today because of their lack of structure and efficiency within the conduct of clinical research studies. In fact, most of the negative media reporting of late has stemmed from the lack of oversight of the research that is conducted at prestigious academic centers.

Over the past decade, academic institutions have lost a great deal of their industry funding for studies that now go to such organizations as site management organizations (SMOs), contract research organizations (CROs) and dedicated clinical sites. Academic centers in the USA are attempting to improve their reputation in conducting efficient clinical trials by centralizing offices for

clinical studies, partnering with CROs, and improving their Institutional Review Board (IRB) process and oversight. Patient recruitment is key to their bottom line success.

Although CROs, SMOs and other dedicated clinical sites are focusing on patient recruitment services, they still use the standard methods of recruitment, such as print, radio, TV and sometimes the Internet, to seek potential volunteers. Added to this mix are public relations campaigns and outreach programs, which are rather expensive. Numerous public relations and marketing firms are now making substantial profits on the patient-recruitment portion of clinical research; however, they are limited in their core capabilities in the research field to address long-term solutions. Specifically, most commercial recruitment companies do not have clinical research expertise on staff to guide them with deep knowledge of the research business, so are thus limited in their capabilities.

Some high-profile companies in the USA that provide expertise in patient recruitment include Patient Quest (Chicago, IL, USA), Americans Doctor (Chicago, IL, USA), BBK Healthcare (Newton, MA, USA), CenterWatch, GCI Healthcare (New York City, NY, USA), Matthews Media Group (Rockville, MD, USA) and Pharmaceutical Research Plus (Baltimore, MD, USA). Although some of these companies are niche-oriented and focus solely on patient recruitment and retention, others are broad-based and offer services in several other areas. Another way in which these companies are differentiated is their approach to patient recruitment and retention. Some companies rely largely on consumer advertising methods, whereas others emphasize approaches that are driven by patient and investigator needs. Thus, these companies might be advertising centric or patient–physician centric. Regardless of their approach, the primary measure of success of companies focusing on patient recruitment is the metrics resulting from their efforts. If metrics demonstrate that they have in fact expedited the study, successfully filled the study patient-number requirements, or reduced study completion time, then they have been successful in their strategy. Companies that focus on their relationship with the sites seem to hold the key to the successful and timely completion of a study.

Another type of business entity that is involved in patient recruitment services is the independent call center. Independent call centers have been around for more than a decade and offer a variety of services, from initial patient screening to scheduling of visits and media and advertising assistance. An effective call center can expedite the recruitment process, whereas an ineffective one can complicate the process. Some US-based call centers include Alliance Marketing (Marion, IA, USA), Pharmaceutical Research Plus (Baltimore, MD, USA), TeleRX (Horsham, PA, USA), and Pharmatech Solutions (Wilmington, NC, USA). In addition, some large CROs have brought call centers in-house through acquisitions.

High tech eRecruitment – is it working yet?

The newest players in this fray are the eClinical trial entities. Although many more new entities are focusing on patient recruitment, it does not necessarily make the process more efficient or more successful. A Forrester report projects that general Internet use will continue to grow, reaching 76% of US households and 47% of European consumers by 2005, and that it should become a logical forum to attract patients to studies [8]. However, Forrester researchers are also critical of those companies that attempted to recruit patients via the Web over the past few years. They note lack of brand, content and functionality as the key issues for failure to recruit patients via the Internet. Companies with Internet components to their recruitment strategy or developing strategy include CenterWatch, WebMD, Acurian, ClinicalTrials.com, Quintiles and PPD, among others. Interestingly, Forrester's analysis highly ranked two websites provided by the US federal government (NIH) – Emerging Med and Cancer.gov [2].

Because of a dearth of funding, innovation and proof-of-concept, it will take another few years to see significant progress in the eRecruitment arena. Added to this, the traditional lack of adoption by PhRMA to eTechnology will slow this development process. The major hurdle that industry will face is the integration of various technologies into their existing systems or lack of systems. For technologies to truly be of value, they should increase efficiencies, decrease development time and provide innovation beyond the existing and antiquated processes.

What about the patients?

Several recent studies suggest that fewer patients are responding to recruitment promotions and fewer are now completing clinical trials [9]. Recent media articles have profiled scandals within the clinical trials industry, with investigators depicted as greedy and criticized for being paid for the study work they do in clinical trials. At a few academic institutions in the USA, studies have been temporarily closed because of a lack of oversight by their IRBs and have been highly profiled in the media. Unfortunately, patients and potential study volunteers worldwide are not getting a balanced perspective from the media about the advantages of participating in clinical research. Little education has been provided by industry and physicians alike to counter the effects of negative reporting, thereby causing a greater challenge in recruitment.

Clearly, it is essential to get the message across to the media and the public that patients enjoy important benefits as participants in clinical trials, such as:

- Access to newer, potentially better treatments as well as access to highly qualified practitioners.
- More attentive care from physicians and other healthcare professionals because of their participation in the trial.
- Relief from research related medical expenses because their research related care is paid for by the trial sponsor.
- Better education about the disease and its management.

Indeed, most patients feel that they have been better treated, better regarded and better educated in clinical trials than under the care of their primary care physicians [10,11]. More than half of all study subjects rate their experience in clinical trials as excellent and another 34% rate their experience as good. Less than 4% report having a poor experience and three out of four study volunteers say they would definitely participate in a clinical trial again [11].

Clinical trials also afford substantial benefits to those physicians who serve as investigators. These advantages, however, are sometimes masked by a cloud of challenges or criticisms, for example:

- Most investigators are doing double duty, caring for their patients in private practice as well as conducting clinical trials. Although, at first glance, this appears to be an undesirable situation, closer inspection reveals that this commitment provides a foundation for attaining respect from both outside and within the medical community. Indeed, investigators should be embraced for their extended efforts and dedication to providing improved treatment options for patients.
- Investigators are often criticized by those outside the medical community as being biased toward the drug sponsor that pays them. In truth, clinical trials consist of well-designed, controlled studies that typically excel at gathering objective, nonbiased data. The fact that investigators receive financial renumeration for their work only serves to better ensure that they will perform at optimal standards.
- A common misconception is that physicians who conduct clinical research usually incur greater liability. Although the potential exists for increased litigations because of the use of experimental treatments, experience shows that less litigation occurs in clinical trials than in private medical practice.
- A major benefit – one that is recognized by healthcare practitioners but rarely addressed by the media – is that physicians who are involved in clinical trials are better informed on the latest therapies and research. Emphasizing this point with the media and public could enhance patient recruitment, because patients would find it appealing to know that the study's physicians are highly knowledgeable in their disease and the latest advances in treatment.

Indeed, the winners or losers in the arena of patient recruitment are clearly the patients, depending on how the studies are conducted and completed. If the patient is a 'winner' in this process, then so are the sponsors of the studies who are positioned for potential tremendous financial gain. It is imperative that the industry or governments that sponsor studies, as well as the physicians who treat patients, be engaged and committed to all of the processes surrounding this complex and challenging effort in patient recruitment. This means that innovation, whether it is new technology, systems or strategy, be placed at a priority level by those involved in this patient recruitment process. Patient recruitment has been treated as a lower priority in the clinical research process for too long.

References

1 CenterWatch (1999) *An Industry in Evolution*. (2nd edn), p. 264
2 Barrett, M.J. (2001) *The Forrester Report: eRecruiting for Clinical Trials*. pp. 3–20, Forrester Research
3 Ackerman, J.D. and Simon, J.P. (2000) In *e-Pharm: Accelerating Clinical Trials and Enhancing Details: Industry Analysis*. pp. 3–44, Friedman, Billings, Ramsey & Co.
4 CenterWatch (2000) Another setback for CROs. 7 (April), pp. 11–16
5 CenterWatch (2001) Reflections on 2000. 8 (January), p. 1
6 CenterWatch (2001) Anticipating a clinical investigator shortfall. 8 (April), pp. 1, 5–13
7 Drennan, K.B. (2001) Have the ultimate benefits of clinical trials been maligned beyond repair? *Drug Discov. Today* 6, 597–599
8 February 2000, *The Forrester Report: The Ubiquitous Internet*. Forrester Research
9 Getz, K. (2001) In *A Guide to Patient Recruitment*. p. 34, Danderson
10 Drennan, K. (2000) Letter to the editor. *CenterWatch* 7 (November), p. 4
11 CenterWatch (1999) A word from clinical trial volunteers. 6 (June), p. 1 and 9