

# CURRENT CHALLENGES IN CLINICAL TRIAL PATIENT RECRUITMENT AND ENROLLMENT

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**Abstract:** *Achieving clinical trial research participant enrollment is essential to conducting a successful trial. Adequate enrollment provides a base for projected participant retention, resulting in evaluative patient data. Without sufficient patient retention from the time of study initiation to closeout, the number of remaining participants may prove to be too small a pool from which to derive conclusive proving or disproving the goal of the clinical trial sponsor. Obtaining final evaluative data is dependent on successful patient and principal investigator retention. Patients cannot be retained without an initial pool of enrolled volunteers. This initial pool of screened, then enrolled participants, depends on designing sound strategies for patient and investigator recruitment.*

## **Introduction**

“Competition within the pharmaceutical industry continues to intensify, and competing for clinical investigators and patients is no exception. While pharmaceutical companies invest heavily in marketing approved drugs, they often do not employ that same market research and marketing expertise when it comes to targeting, positioning and communicating the value of clinical trials to study sites and patients. The research data underscores the high stakes and urgent need for pharmaceutical companies to improve the clinical trial process. Effective communications can result in better-selected study sites and patients who will remain with a study until it is completed, saving time and money in clinical trials.”<sup>1</sup>

Achieving clinical trial research participant enrollment is clearly essential to conducting a successful trial. Adequate enrollment provides a base for projected participant retention, resulting in evaluative patient data. Without sufficient patient retention from the time of study initiation to closeout, the number of remaining participants may prove to be too small a pool from which to derive conclusive proving or disproving the goal of the clinical trial sponsor. Obtaining final evaluative data is dependent on successful patient retention. Patients cannot be retained without an initial pool of enrolled volunteers. This initial pool of screened, then enrolled participants depends on designing a successful patient recruitment strategy. “A major focus in all clinical trials in the recruitment of subjects. Where and how to do this depends on the demographics of the target population and the condition under investigation.”<sup>2</sup>

Until publication in 1992, there had been “no systematic guide to use for recruiting human subjects for clinical studies, although difficulty in patient recruitment is the major reason for failure of clinical trials”<sup>3</sup>. Patient Recruitment in Clinical Trials, authored by Bert Spilker and Joyce Cramer, provided the industry with the first published template for the development of a successful clinical trial recruitment plan.

“In this volume, two renowned experts guide investigators step-by-step in developing and implementing a strategy for successful patient recruitment. The authors detail practical approaches to preventing or solving the problems that can arise in every phase of the recruitment process - from identifying sources of patients, requesting referrals from physicians, contacting and screening patients, and obtaining informed consent, to training a recruitment staff,

budgeting costs, establishing goals, assessing progress, and rescuing a clinical trial that is not reaching patient recruitment goals. The book contains samples of newspaper advertisements and brochures used to recruit patients, newspaper stories published in response to press releases about clinical trials, letters sent to physicians to request patient referrals, and other materials that can serve as practical models. The authors also offer advice on publishing patient recruitment data and explain how such data affect the extrapolation of clinical trial results.”<sup>4</sup>

Combining published templates for successful recruitment strategies with an understanding of participating sponsor, Principal Investigator, and subject perspectives will contribute to the successful completion of clinical research trials.

#### **Sponsor Perspective**

A research participant enrollment goal is established far in advance of trial initiation. This target number is documented in the trial protocol as “N,” the number of desired participants. Those who design the protocol expect some initially recruited volunteers to become screen failures and not continue to randomization onto study drug. A reasonable expectation is that others will drop out of study participation due to factors such as consent withdrawal, poor protocol compliance, or the occurrence of serious adverse events that are deemed to mandate study withdrawal. Those who design the study plan must specify a larger number “N” in the protocol than the number of participants expected to be evaluative at study closure.

As the so-called “Louis Lasagna” rule or “Muench’s Third Law” indicates, the recruitment strategy must be one that reaches again a greater

number of potential participants, as a fraction of potential participants will progress first to the screening phase, then progressively smaller numbers to randomization and finally study conclusion. For example, in a study of recruitment and retention in a trial of low birth weight premature infants, it was concluded that “successful recruitment was largely due to attention and resources allocated to ensure that all potential participants were approached and that enrollment and retention were high. High recruitment and retention rates were attributed to the intense effort by the national coordinating center to provide detailed training, written protocols and on-site monitoring to help clinical center staff in their recruitment and retention planning and process.”<sup>5</sup> Frequently, a suitable patient population initially appears to be available for a target indication. Recruitment and enrollment difficulty ensues when detailed protocol inclusion/exclusion criteria drastically narrow the population qualified to participate.

According to the Healthcare Communications Group, a clinical trial recruitment strategy and advertising contractor, “To bring new drug compounds to market efficiently, pharmaceutical manufacturers must generate substantial numbers of qualified study participants within the clinical trial process at the lowest cost possible.”<sup>6</sup> The goal of a sponsor company in conducting a successful clinical trial is to gain a New Drug Application approval from the Food and Drug Administration by the most efficient methods while maintaining an ethical standard of trial participant management. The responsibility of the sponsor is to either directly recruit participating Principal Investigators and volunteers or contract such services through a Contract Research Organization and/or recruitment-advertising agency, such as the Healthcare Communications Group.

No matter which of the above organizations implement the strategy, both Investigators and participants must be identified and successfully recruited. “Previous research by UC Davis Cancer Center investigators, published in the March 13, 2001 issue of the *Journal of Clinical Oncology*, found that both doctors and patients sometimes hold misconceptions that can discourage enrollment in clinical trials. In that study, more than a third of the doctors declined to refer patients to clinical trials, mistakenly believing that no trials were available or that their patients were too sick to be accepted. In reality, more than 150 clinical trials were available during the study period.”<sup>7</sup> The success of a clinical trial depends on efficiently recruiting suitable participants from the medical community to conduct the trial and from the general public to participate in the trial.

#### **Principal Investigator Perspective**

Clinical trial participation can be a lucrative opportunity for potential investigators. Participation allows physicians to be on the cutting edge of medicine, even if the physician is involved with a small family practice instead of with a traditional large academic research institution. In recent years, the “pharmaceutical industry has switched from career researchers at academic medical centers, whose professional reputations are forged on quality of their data, to thousands of private-practice doctors to whom testing has become [an] extremely lucrative sideline.”<sup>8</sup> The Principal Investigator is the link between the patient and the sponsoring pharmaceutical company. Therefore, a prime goal of the sponsor is to successfully recruit qualified Investigators.

The sponsor appeals to potential Investigators intellectually and monetarily when recruiting physicians. Commonly “drug companies and contractors offer

large payments to doctors, nurses and other medical staff to recruit patients, some getting finder's fees for merely referring patients to studies..."<sup>8</sup> "This activity is strenuously frowned upon in academic institutions and absolutely discouraged. In some rare instances the referring physician (usually a resident) will be given a 'low-cost' gift certificate to the medical bookstore."<sup>9</sup> Frequently, Investigators receive higher financial rewards when they quickly recruit patients, such as for competitive enrollment studies. The Office for Human Research Protection is "concerned that excessive compensation may motivate [Principal Investigators] to 'cram' subject into studies, thereby compromising informed consent standards."<sup>10</sup> Care should be taken by all parties involved, i.e., the sponsor, the contract research organization, FDA, the investigator, the clinical research associate, and indirectly the patient, to strive towards the balance between contributions to the study and the resulting compensation. Controversy arises when this balance is compromised. This controversy then fuels distrust from the public and the medical community, thus influencing the success of both subject and Investigator recruitment.

"According to a 2002 Harris Interactive poll commissioned by The Summit Series on Cancer Clinical Trials, 83% of adults believe that clinical trials are essential or very important. So why do only about 3% of oncology patients in the United States enroll in clinical trials? Ongoing public misconceptions of clinical trials - often exacerbated by negative press - and reluctance on the part of some healthcare professionals to enroll patients for a variety of reasons play significant roles."<sup>11</sup>

Successful recruitment of investigators translates into recruitment of patients. "Recruitment is a two-step process. It requires the recruitment of general practitioners followed by the recruitment of patients. Potentially, there is access to large numbers of general practitioners. Strategies for the recruitment of general practitioners include advertising, incentives, personal contact, and establishing a network."<sup>12</sup> Similar strategies hold true as well for trial volunteer recruitment.

The sponsoring company usually recruits Principal Investigators through company databases of those who previously conducted trials in the given indication, through similar databases retained by the contract research organization, by word-of-mouth through clinical research associates who previously monitored for a study of a similar indication, and by word-of-mouth in the medical community.

One of the two most common avenues of patient recruitment is through direct advertising campaigns by the sponsor or advertising agency to the potential participant, as noted above. The potential participant responds to the sponsor or agency after being notified of the study by newspaper, radio, possibly television, or eventually word-of-mouth advertising. "Patient recruitment advertising is a complex process. The difference between a successful and unsuccessful recruitment campaign is dependent on the study's enrollment criteria, the clarity and execution of the creative advertising message, the intelligent targeting and spending of the medial budget, and how well prospective patients are handled once they respond to advertising."<sup>13</sup> The potential volunteer is then redirected to a participating Principal

Investigator. "Trials are [frequently] conducted in a general practice setting because for many target groups or conditions, that is where the appropriate patients (subjects) are to be found. As well as this, these subjects may be more representative of the range of patients in which the target condition exists, or for whom the technology is applied or the drug is used."<sup>14</sup>

The other main way to reach potential research participants is directly through the Investigator's practice. The Investigator himself/herself or supporting staff members may approach individuals already in their practice with medical histories/new diagnosis of the target drug indication (for phase I-IV studies). "The fact that many [primary care physicians], surgeons, and other members of the healthcare team do not encourage their patients to consider participation in clinical trials also contributes to low enrollment. Results from one study showed that a recommendation by their physician was the primary factor influencing patients' decisions to enroll in a trial."<sup>15</sup>

The National Cancer Institute succinctly details the following common perceived barriers that the medical community claims in regards to clinical trial participation.<sup>16</sup>

- **Lack of awareness of appropriate clinical trials.** Physicians are not always aware of available clinical trials. Some may not be aware of the local resources, or some may assume that none would be appropriate for their patients.
- **Unwillingness to "lose control" of a person's care.** Most doctors feel that the relationship they have with their patients is very important. They want what

is best for the patient, and if the person must be referred elsewhere to participate in a trial, doctors fear they may lose control of the person's care.

- **Belief that standard therapy is best.** Many health care providers may not adequately understand how clinical trials are conducted or their importance. Some believe that the treatment in clinical trials is not as good as the standard treatment. [Investigators] might be uncomfortable admitting that there is uncertainty about which treatment is best in a phase [III] clinical trial.

Debora Paterniti is an Assistant Professor of general medicine at the UC Davis School of Medicine and Medical Center and author of a study that monitored cancer patients as they considered participation in Phase I and Phase III trials at the UC Davis Cancer Center.<sup>17</sup> Paterniti found that "...a third of patients who were considered for clinical trial participation declined to participate, many of them out of a mistaken belief that investigational treatments are not as effective as standard treatment. In fact, many investigational treatments as at least as effective as conventional therapy, and cancer patients who participate in clinical trials frequently have higher survival rates than those who receive standard care."

- **Belief that referring and/or participating in a clinical trial adds an administrative burden.** The length and details of most research protocols may deter providers from participating in clinical trials. The possibility of incurring additional costs and expenses that might be inadequately

reimbursed is a deterrent for many.

"According to a study survey conducted in 2000 by the American Society of Clinical Oncology (ASCO), the most significant barriers to patient enrollment included the intensity of paperwork collection and filing, and the extra time needed to train staff in the completion of enrollment and data collection forms."<sup>18</sup>

"Recruitment and adherence are very closely linked since those recruited must be followed to study completion as the inception cohort. ... There is a clear impact on recruitment in terms of cost and both screening and staff burden."<sup>19</sup>

Sponsoring companies, through increased industry education, can address the above-mentioned perceptions. The drawback to this simple solution is that increasing awareness in the medical community is far easier to accomplish in theory than in practical application. More accurate information regarding trial participation from the Investigator's perspective is readily available on the Internet, by word-of-mouth from practicing clinical research Investigators, and from sponsoring companies. For example, Investigator reluctance to relinquish authority over patient care can be addressed when the Investigator considers that he/she retains the authority to ultimately control the progress of patient care during study participation. The PI may discontinue patient from the study at his/her discretion if he/she feels patient care to be compromised.

The Investigator and his/her staff hold the responsibility of conducting the informed consent process prior to initiating any study procedure with the volunteer. "It

is crucial that physicians ensure that patients' needs - such as having their questions answered and being offered a sound rationale for a particular study - are met, especially as patients tend to decide quickly whether or not to participate in clinical trials."<sup>20</sup> "Complicated consent forms alone often provide little meaningful information to patients who are considering participation in a trial, do not serve their purpose successfully, nor encourage enrollment."<sup>21</sup>

The Investigator works with the potential participant to explain study procedures, emphasize that trial participation is strictly voluntary and that consent may be withdrawn by any time by either the volunteer or the Investigator, detail possible risks, provide 24-hour emergency contact information, and provide sufficient time for the potential participant to ask questions. Properly conducting the informed consent process develops an ethical rapport between Investigator and participant. This process cannot begin and participants cannot be initiated into the study if patients are not successfully recruited.

### **Clinical Research Volunteer Perspective**

"If we are to expedite drug testing and widespread availability of approved drugs, we must increase patient recruitment into clinical trials. There are many opportunities to encourage patients to enroll in clinical trials so they feel confident about their decision to do so. One way is to improve the way we communicate with patients and with other healthcare professionals about the importance of these trials. We need to ensure that patients know their treatment options and understand the risk and benefits of clinical trials so that, together with their physician(s), they can make informed decisions about the care most appropriate for them."<sup>22</sup>

Only by introducing physicians to the process early in their careers will they become more receptive to clinical trial participation. "However, medical schools have failed to provide students with even rudimentary information concerning the importance and structure of clinical trials, let alone teach them that clinical trials play major role in transforming the practice of medicine from an art to a science by replacing anecdotal information, which has so often influenced therapeutic decision making, with more credible and substantive data for selecting a therapy."

Barriers from the perspective of the potential volunteer are common both in assumption and in reality. Paterniti notes that there are "five broad categories of potential barriers to participation: lack of resources on the part of patients' health insurance restrictions; confusion about the difference between research and medical care; confusion about study procedures; and misunderstandings of the illness and its severity. The observations also turned up three potential barriers to truly voluntary participation by patients: desire on the part of a patient to please a family member or physician, a feeling by the patient that no other options exist; and perceptions by patients that they are required to be in a clinical trial." Each concern found by this study can be addressed again by properly conducting the procedure of informed consent, leading to enrollment of a participant who is comfortable with the ethical rationale of signing the informed consent form.

The National Cancer Institute again details the following common barriers that potential volunteers consider in regards to clinical trial participation.<sup>23</sup>

- **Lack of awareness of clinical trials.** Research has consistently shown that most people with

cancer are not aware of the option to participate in clinical trials.

- **Lack of access to trials.** The reality or the perception that there are no trials nearby deters many potential participants. In addition, seeking care at a distant trial site presents time and travel barriers.
- **Fear, distrust, or suspicions of research.** For many people, the loss of control (not choosing their treatment) that comes with entering a randomized trial is too great. Many also fear being treated like "guinea pigs" or being "experimented upon," as well as not receiving treatment for their cancer. People may have a general lack of trust in the medical profession based on past negative experiences or the knowledge of historical abuses of research participants.

The media plays a significant role in fanning the flames of such public suspicion. It is inarguable that recent high-profile media coverage of ethical breaches and improper monitoring of clinical research, for example at Duke and the University of Pennsylvania, resulted the public being both simultaneously informed and misled. The public was informed of current events in clinical research from such exposes, however was left fearful of participation. Unfortunately, additional education touting the positive aspects of research did not accompany such sensational news stories. Naturally the public pool of potential volunteers is left fearful, distrustful, and suspicious of considering participation. As of April 14, 2003, the Health Insurance Portability Accountability Act (HIPAA) is to provide additional protection against fear of medical records privacy loss. HIPAA was publicized on national news media during the week of April 14, 2003. From this date onward, informed consent forms containing a HIPAA

clause or a separate HIPAA form must be signed by the volunteer prior to the initiation of any study procedure. Properly executed, the creation of HIPAA will contribute to reversing such distrust of the healthcare system, including clinical research.

Whereas barriers arising from lack of awareness of clinical trials, lack of access, distrust, and hesitation to participate from perceived relinquishing of autonomy may be addressed through increased education, practical/personal challenges also exist that significantly influence the recruitment and enrollment strategy. Richard L. Schilsky, author of *Conversations in Care*, notes that "family members' negative attitudes or perceptions of clinical trials can dissuade patients from enrolling. Frank, sensitive dialogue with family members is often helpful in countering their concerns or misconceptions about what is involved in clinical trials. ... Other factors that influence a patients' decision to accept or decline clinical trial participation include time constraints, distance from study site, transportation issues, and interference with work or home responsibilities. It may be appropriate for other members of the healthcare team, such as social workers, to assist patients in dealing with these issues."<sup>24</sup>

- **Practical or personal obstacles.** Costs of being away from work and family may be deterrents for some people. Others may not wish to leave the care of their own physician. People from certain racial or ethnic groups or who are medically underserved may feel that care within a trial will not be sensitive to their needs. Others may feel that recruitment strategies are not sensitive to their needs. Still others may believe that standard care is better than the treatment available in a trial.

- **Insurance or cost problems.**

Another deterrent is the fear of being denied insurance coverage for participation in a clinical trial. If a person is uninsured, the cost of trial participation is an issue.

Schilsky explains how the “lack of insurance coverage (or fear that they will not have coverage) is often a significant problem to patients. Results from a [National Cancer Institute] study showed that patients with fee-for-service coverage were more than twice as likely to enroll in trials compared with other types of coverage, including managed care.”<sup>25</sup>

- **Unwillingness to go against personal physician’s wishes.**

The Investigator and his/her supporting staff, as well as the referring primary care physician, if applicable, must take care to educate patients that participation is the patient’s decision, not that of the doctor. Documentation that the patient waived his or her rights to decide is not usually acceptable.

Under-represented populations have noticeable hesitation to enroll in clinical trials. Historical incidents of mistreatment of minorities for research trials, such as the infamous Tuskegee syphilis study, leave powerful impressions in the public eye. For example, “middle-class, professional African-American women interviewed in one study stated that they would consider joining a trial if the trial was relevant to their medical needs and if there were asked to do so.”<sup>26</sup> As many as one-third of African-American women in another study avoided participating in clinical trials because they believed that scientists cannot be trusted, while 37% expressed a preference to be

treated by an African-American physician. Furthermore, only 28% felt that clinical research in the United States is ethical.<sup>27</sup> African-American men in another study said they would be more willing to participate in prostate cancer clinical trials if they were encouraged to do so by competent and compassionate clinicians.”<sup>28</sup> Physicians need to recognize these serious concerns, address them, and then confidently recommend studies that are the most appropriate. Effective communication that promotes patients’ trust and confidence in their physicians is a powerful motivating influence.”<sup>29</sup>

“Under the bioethical principle of beneficence, all biomedical research should be designed to maximize benefit and minimize harm (McCarthy 1994). Limited clinical trial participation among women and minorities can lead to harm through denying these groups critical information that could alter ineffective or detrimental medical care (Dresser 1992). There is an urgent need for information that will lead to the identification and validation of cancer control interventions for minority populations (Alexander 1995). Many of these populations suffer higher cancer rates than the majority population. Therefore, it becomes imperative that all groups of people including women and minorities have equal access to the advantages that participation in clinical trials brings (NIH 1994a, Spilker and Cramer 1992, Wermeling and Selwitz 1993). ... In our effort to include minorities and women in clinical research, the medical community must recognize that some people within these groups may be vulnerable or less advantaged and need special recruitment consideration and safeguards (NIH 1994b, Spilker and Cramer 1992).”<sup>30</sup>

The National Cancer Institute again explains several common barriers that underrepresented groups give as reasons to not become trial participants.<sup>31</sup>

- **Long-standing fear, apprehension, and skepticism** exist among some minority populations about medical research because of abuses that have happened in the past (e.g., the legacy of the Tuskegee syphilis study). Among these populations, there is often widespread fear and distrust of the medical care system as a result of discrimination, indifference, and disrespect. Many feel that they do not want to give up rights or lose power in order to be “experimented on.” Others may be skeptical about the quality of care that would be provided in a clinical trial. Some may find that trial recruitment strategies are not sensitive to their needs.
- **Doctors may not mention clinical trials as an option for cancer care.** As noted above, many physicians do not refer people to clinical trials. Some physicians may avoid suggesting a clinical trial to people who belong to racial or ethnic minorities out of concern that people would see them as insensitive. Moreover, some physicians may inadvertently discriminate against older people or those from certain ethnic or cultural backgrounds.
- **People from various cultural or ethnic backgrounds hold different values and beliefs that may be different than principles of Western medicine.** Many people have cultural beliefs that Western medicine cannot address their health concerns. Different ethnic and cultural views of health and disease (e.g.,

fatalism, family decisions about treatment, use of “traditional healers,” prayer, herbal medicines, or use of complementary/alternative health practices) may make clinical trials a less attractive treatment option. For prevention trials, many may feel that the risk of a potential disease and its consequences may be less important than meeting daily needs.

**Language or literacy barriers may make it difficult for some people to understand and consider participating.** The complexity of forms, including informed consent documents, may also be a barrier to those considering participation. Translation can also be difficult if the person translating information has not had specialized training.

**Additional access problems confront many people.** Depending on where they live or their access to transportation, people may have difficulty getting to a clinical trial site. Those with low incomes may find it difficult to take time off work or find appropriate childcare. Other barriers, such as a lack of health insurance or a source of health care, clearly present difficulties in accessing trials.”

Medically underserved groups include racial and ethnic minorities and extend also to those who live in rural areas with little access to medical care, those with low income or literacy, and homeless individuals. Homeless individuals who volunteer to participate in clinical trials present an ethical complication that presents itself in addition to lack of access or education. Participation frequently involves monetary compensation for the Investigator as well the volunteer. Trial participation is known within homeless populations located in areas

proximal to medical research centers and university hospitals to be a reliable source of income. Although sponsoring companies aim to include a wide variety of individuals who fit study inclusion/exclusion criteria, so as to find drug data that represents the effect of the drug on the general public, safety concerns may arise. These concerns for both participant safety during the course of the trial and for the public, should the drug reach the open market, arise when volunteers give false answers regarding inclusion/exclusion criteria and deny the occurrence of adverse events and/or serious adverse events, for fear of losing monetary compensation.

Additionally, university students are commonly known to be frequent

trial participants. As with homeless individuals, participation in clinical trials provides a lucrative source of quick income. Whereas homeless individuals and university students are rewarded with money, homeless individuals find the stay in a safe environment with meals provided during in-patient studies to be an attractive additional benefit, while students are often “treated” to exotic clinical site locations, often during the Spring Break season. The break from basic survival for the homeless and the mini-vacations for students can be lucrative enough to encourage the potential volunteer to not be entirely truthful when completing the informed consent process.

### A Survey on Clinical Trial Barriers

A survey of almost 6,000 people with cancer conducted in 2000 took a look at why so few adults participate in cancer clinical trials. Some of the highlights included:

- About 85 percent of people with cancer were either unaware or unsure that participation in clinical trials was an option, though about 75 percent of these people said they would have been willing to enroll had they known it was possible.
- Of those who were aware of the clinical trial option, most declined to participate because they believed common myths about clinical trials.
  - They either thought that:
  - The medical treatment they would receive in a clinical trial would be less effective than standard care.
  - They might get a placebo.
  - They would be treated like a “guinea pig.
  - Their insurance company would not cover costs.

People who received treatment through a clinical trial found it to be a very positive experience:

- Ninety-seven percent said they were treated with dignity and respect and that the quality of care they received was “excellent” or “good.”
- Eighty-six percent said their treatment was covered by insurance.

## Conclusion

Health care providers, clinical trial sponsors, the media, and the public must maintain open communication to overcome real and perceived barriers to clinical research participation. Carefully planned design, implementation, and follow-through of sound recruitment and enrollment strategies contribute to the efficiency and success of clinical research trials from initiation to study close-out.

The following findings from the Harris Interactive poll are of additional interest.<sup>32</sup>

## Footnotes:

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