Patient Recruitment in Cancer Clinical Trials
A DAVA Oncology White Paper

Introduction
Study delays are a significant problem in clinical trials in general, and in cancer clinical trials in particular. These delays are cumulative, extending from the initial time of site identification through the site startup process and ultimately to study enrollment. Even when delays in startup are accounted for and minimized in the planning of a clinical trial, the problem of slower than anticipated enrollment at individual participating study sites remains. Most clinical trials enroll at rates that are slower than anticipated during the planning process, and a significant number of sites fail to enroll a single subject. A recent study demonstrated that 38.8% of cooperative group trials and 20.6% of non-cooperative group trials failed to accrue a single patient.1

Entire books have been devoted to the subject of patient recruitment, but despite the fact that oncology is the largest therapeutic area in clinical research there has been relatively little published on how to best recruit patients for cancer clinical trials.

What Makes Cancer Clinical Trials Different?
One of the most important factors influencing patient recruitment in cancer clinical trials is the nature of the disease itself. There are over 200 well-described types of cancer, which are generally defined by the tissue of origin and histological/cytological criteria. Beyond this, a high degree of heterogeneity exists within individual cancer types. Human breast cancer, for example, is a group of at least 10 distinct subtypes, each of which possesses a unique molecular and/or biochemical signature, clinical course, and prognosis.2 Molecularly targeted therapies, which target these molecular and biochemical signatures, are the most common class of drugs in clinical development. Most of the recently approved therapeutic agents for cancer fall into this category.

The advent of molecularly targeted therapies has led to clinical trials that are focused on small populations, even when the therapy is for a common form of cancer. For example, a clinical trial of an EGFR inhibitor for metastatic non-small cell lung cancer (NSCLC) might be focused only on the EGFR mutated population, which represents 10-20% of the overall NSCLC population. This, of course, makes enrollment more difficult since the pool of eligible patients is much smaller than in trials for unselected patients.

A less appreciated factor that influences recruitment to cancer clinical trials is the nature of clinical care for cancer patients. Cancer is, in most cases, a life threatening disease for which there is a real or perceived urgent need for treatment. In addition, the diagnosis and decisions made with regard to therapy are a source of tremendous fear and uncertainty for cancer patients. Because the clinical trial consent and screening processes can take a significant amount of time, in some cases this urgency can lead physicians to offer standard therapy that can be started quickly as opposed to participation in a
clinical trial. This can occur even when the need to begin treatment quickly is less medical than psychological, i.e., the need to “do something quickly”.

Even when the issue is not urgency of starting treatment, there are barriers that influence how likely physicians are to refer patients to trials. One of these is the availability of a clinical trial at the physician’s own institution or practice. If the treating physician is an investigator on a clinical trial for which the patient is eligible, in many cases the patient will be offered a clinical trial and will potentially enroll. In other cases, in which the treating physician is not an investigator or does not have the trial top of mind, the likelihood of the patient being offered clinical trial participation is lower.

Another significant factor is a physician’s bias with regard to particular forms of therapy based on personal experience, which may not be supported by the scientific literature. When these biases are not compatible with the design of a clinical trial (for example, when the comparator is a treatment the physician does not often use), recruitment to a trial from the physician’s practice is likely to be poor. Conversely, when a clinical trial sponsor chooses a comparator that isn’t considered “standard of care” by the majority of practicing physicians, slow recruitment is essentially guaranteed.

With this background, the goal of patient recruitment strategies for oncology trials should be to make sure that the trials are well designed, compatible with current patterns of care and that all potentially eligible patients have both the opportunity to participate and ready access to accurate and unbiased information, presented in a way that minimizes complexity without hiding important information that may influence decision-making.

**Strategies to Enhance Patient Recruitment in Cancer Clinical Trials**

**Online resources**

In this era of widespread internet access, online resources are commonly used by patients and caregivers when searching for information on treatment options, including clinical trials. General clinical trial information is available at several well-known websites, most notably [www.clinicaltrials.gov](http://www.clinicaltrials.gov). This website, a service of The U.S. National Institutes of Health (NIH), is provided through the National Library of Medicine. All trials that involve drugs, biological products, or devices that are subject to FDA regulation are required to be registered. The International Committee of Medical Journal Editors (ICMJE) has also established a requirement that all clinical trials be entered in a public registry (such as clinicaltrials.gov or the EU Clinical Trials Register) before the onset of patient enrollment as a condition of consideration for publication. The requirement for registration of clinical trials has helped to ensure that information is available for all clinical trials that are being conducted. It has, however, created a potential problem with “information overload”, in that patients and caregivers may identify hundreds of clinical trials for their condition without a way to prioritize the trials that are most appropriate for their individual situation.

In association with TrialCheck®, the American Cancer Society ([www.cancer.org](http://www.cancer.org)) now offers a clinical trial matching service for cancer patients. Although on recent testing the website was not functioning properly, the site purports to match trials on the basis of detailed eligibility criteria. It does not, however, attempt to otherwise prioritize trials.
Another important source for cancer information is www.cancer.gov, the website of the National Cancer Institute (NCI). This website provides information on many types of cancer, clinical trials, and common questions. In addition, this website provides a help line (1-800-4-CANCER) and a “LiveHelp Online Chat” to answer questions. The service presents clinical trials as one available treatment option, explain the process, risks, and benefits of trial participation, and provide links to lists of clinical trials specific to disease stage and zip code.

The Center for Information and Study on Clinical Research Participation (CISCRP) is a nonprofit organization dedicated to educating and informing the public, patients, medical/research communities, the media, and policy makers about clinical research and the role each party plays in the process. CISCRP offers a clinical trial matching service based on medical condition and geography. A toll-free number (877-MED-HERO) is also provided to assist with clinical trial searches.

Social media also has the potential to provide useful information about clinical trials; however, the inabilities of sponsors and investigators to manage messaging and conversations about a trial and concerns about confidentiality and privacy have thus far limited its impact. Patient communities, such as www.patientslikeme.com, have begun to discuss clinical trial participation and also provide a clinical trial listing that allows patients to narrow search according to disease, age, sex and geography.

**Advocacy groups**

Advocacy groups and their respective websites can provide a valuable resource for patients with specific forms of cancer. The Multiple Myeloma Research Foundation, for example, provides a searchable database that contains easy-to-understand information on more than 130 clinical trials. The high number of visitors to the site is thought to have played a role in the rapid accrual to recent pivotal trials involving bortezomib and lenalidomide. The attention that advocacy groups pay to clinical trials is highly variable. The American Association for Cancer Research website (www.aacr.org) has links to 101 support and advocacy group websites. Of these 101 websites, only 24 have clinical trial search engines or trial matching services and 63 prominently offer information on clinical trials. When Kelahan et al surveyed 373 research organization and advocacy group websites, “only 3% provided enough info to potentially overcome the most important barriers to patient participation – lack of awareness about clinical trial availability, benefits of participation, and health benefit coverage – and fully inform visitors about clinical trial options”.

The Army of Women sponsored by the Dr. Susan Love Foundation and the Avon Foundation is exceptional in its emphasis on clinical trials. This program aims to “recruit one million American women as a kind of ‘reservist unit’ that can be quickly called up to the fight by breast cancer researchers who may need their help.” Any woman can sign up on the program’s website (www.armyofwomen.org) to be contacted with research opportunities. If women accept the “call to action” they are directed to an online pre-screener and if they preliminarily qualify are directed to a research site for secondary screening. From its launch in 2008, the website has recruited more than 350,000 volunteers.
Media Advertising
Traditional media advertising (newspaper, radio and television) is commonly used for clinical trials in other therapeutic areas, but has less commonly been used to attempt to increase recruitment to cancer clinical trials. This is primarily due to the fact that media advertising is expensive and that the target market (patients and caregivers) represent a very small fraction of those who are exposed to the advertising, resulting in poor cost effectiveness. Exceptions to this may be cancer prevention trials in which the number of potential subjects is a higher percentage of those exposed to the advertising. In 2004, a mass multimedia campaign was conducted to increase awareness of cancer clinical trials at the University of California Davis Cancer Center. It was observed that clinical trial awareness was increased in the target population after the mass media campaign but this had little impact on actual accrual into cancer studies. 5

Clinical Trial Navigator Services
A large effort was recently made in Florida to increase accrual to clinical trials through the creation of a web and phone based clinical trial navigation service for patients. The service included a verified, state-wide list of open trials that was more comprehensive than clinicaltrials.gov and included patient-friendly trial summaries. The website and phone service were hosted by bilingual clinical trials navigators who helped patients through the education, trial matching, and referral process. Each patient who was matched to a clinical trial received an average of five follow-up calls from the same navigator to help solve logistical problems and provide information, in order to encourage trial enrollment. The effort also included a media campaign to increase awareness of the navigation service. According to Moffitt, “Although we were able to overcome the barriers most commonly cited by patients, enrollment onto cancer clinical trials has not increased significantly. Patients, for the most part, were already receiving treatment by the time they started their search for clinical trials. We decided that taking a strictly patient focused approach was not enough. Coordination with health professionals needed to be addressed to successfully integrate the process of presenting clinical trials as a viable option for patients at a time when patients are likely to be eligible.” 6

Recruiting Underserved Populations
Minority community physicians cite a lack of information about available clinical trials and distrust of the medical centers sponsoring the trials as their primary reasons for not recommending clinical trials to minority patients. The Minority Based Community Clinical Oncology Program (MBCCOP) has had some success in increasing the accrual of minorities to oncology trials by addressing these issues through physician education and community outreach. “Between fiscal years 1995 and 2003, minorities comprised 51% to 67% of the patients accrued (to cooperative group treatment trials) by MBCCOPs compared with <12% of the patients accrued by other CCOPs and <23% of the patients accrued by non-CCOP institutions” 7. The Recruitment, Retention, and Outreach Core at Fox Chase Cancer Center provides investigators access to a productive, collaborative multidisciplinary team of highly skilled recruitment, marketing, education, outreach specialists, and advocacy groups with particular expertise in minority recruitment. Essential to the program was administrative support, appointment of staff with the authority to oversee minority affairs, appropriate infrastructure (adequate time for physician-patient discussion, adequate research staff, and additional support to obtain informed consent), diverse
staff, language banks, acceptance of Medicaid and insurance of minorities. All of these could be quite costly to broadly implement. When RROC was consulted for recruitment to a Prostate Cancer Risk Assessment Program (PRAP), PRAP accrued 59% African Americans, while the primary catchment area was 18% African American.

**Focusing on healthcare professionals**

In 2010 the National Cancer Institute launched AccrualNet (https://accrualnet.cancer.gov/) to serve as a resource for the professional community to support clinical trial accrual. Resources available through AccrualNet include linkable access to existing tools and materials, a searchable list of published journal articles on clinical trial recruitment and space to ask questions, post tips, share experiences, insight, materials and strategies. Training opportunities are also available to orient and educate new staff to successful recruitment strategies.

Since 2007, DAVA Oncology has focused on assisting cancer research professionals with accrual to clinical trials through phone, e-mail and site visits. In the course of these interactions, DAVA’s medical oncologists discuss the trial’s status, diagnose barriers to recruitment and work directly with investigators and research staff to identify strategic actions to overcome these barriers. The ongoing nature of these interactions leads to familiarity of the investigator and research staff with DAVA’s physicians and provides the repeat messaging that is critical to keeping clinical trial enrollment ‘top-of-mind’ with investigators. DAVA’s Accrual Workshops, which are facilitated by one of DAVA’s oncologists, are designed to engage investigators and research staff in interactive, case-based learning activities to enhance accrual. These three to four-hour programs begin with the site attendees presenting their site demographics, including standards of care, referral patterns and accrual potential to their peers. Sites are also asked to present case studies in order to identify appropriate patients for the trial.

As an example of the effectiveness of this approach, DAVA recently participated in a large adjuvant trial in malignant melanoma in which recruitment was increased by over 40% in North America following DAVA’s involvement. The following graphs show specific overall impact of site visits and accrual workshops across 11 different clinical trials:
Conclusion
Study delays are common in cancer clinical trials. Slower than anticipated patient recruitment is a key contributor. There are many reasons for the slow recruitment of cancer patients in clinical trials, including lack of compatibility with current practice patterns, restrictive eligibility criteria, lack of availability of applicable trials, study execution burden and physician bias. Lack of time and resources to properly consider patients for clinical trials is also a significant factor in some care settings. A number of efforts have been undertaken to try to improve accrual to clinical trials in cancer, including widespread availability of internet-based trial registries, clinical trial matching and navigator services, media advertisement and a variety of activities by disease-specific advocacy groups. Despite these efforts, recruitment to cancer clinical trials remains poor. A new approach, focusing recruitment efforts on physicians and research staff through ongoing engagement, holds the highest promise for increasing enrollment in cancer clinical trials.


